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THE DESENSITIZATION OF SKIN SITES PASSIVELY SENSITIZED WITH SERUM OF PATIENTS WITH HAY FEVER. CROSSED REACTIONS OF DIFFERENT POLLENS. THE VARIATIONS IN THE RECIPIENT*

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THE results of treating patients with early hay fever, who are sensitive to trees and grasses, are good, but they are far from perfect. On the whole, they are better than the results obtained in the treatment of patients with late hay fever, sensitive to ragweed, and this is in spite of the fact that almost all of our patients show positive skin reactions to many grass or tree pollens at the same time and that there is no good criterion for the selection of the particular grass or tree pollen to be used in treatment. The problem of selection and the problem presented by the crossed immunologic reactions between the various tree pollens or the various grass pollens, and therefore the possibility of some substance or factor common to many of them, is an old one which has been studied before, but the results of these older studies have been so contradictory and the problem is of such practical importance that it seemed wise to study it once more. In doing so, a number of interesting side observations have been made.

There is reason to believe that certain antigenic substances are in themselves combinations of factors some of which are specific for the original material from which they were derived, while others are common to a group of related materials and substances. Pneumococci, for example, contain type-specific and species-specific antigen. Tuft[1] has demonstrated a factor common to horse dander and horse serum. Simon[2] has described a factor common to all mammalian serums. There is reason to believe that the different pollens of a group may contain a factor common to the members of that group. It is reasonable to consider that the patient may be sensitive either to some substance

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which is specific for one particular pollen, or toward some other factor common to several pollens, or to both the specific and the common factors at the same time. On the other hand, his multiple sensitiveness may depend upon the chance of exposure to a variety of substances not necessarily related. It may be that he is sensitive to several pollens just as he is also sensitive to egg white or wheat or horse dander or kapok and all at the same time.

The presence of multiple sensitivity to grass pollens has been noted by Noon,[3] Freeman,[4] Goodale,[5] Cooke,[6] and many others. Freeman is of the opinion that the various grass pollens furnish one and the same antigen so far as desensitization is concerned. Most authors agree that extract of timothy pollen contains a substance which alone is effective in the treatment of the majority of grass-sensitive cases. Scheppegrell[7] modified this a little by recommending that the choice of extract be determined by the fact that the particular pollen not only gives skin tests, but is common in the patient's environment.

Cooke and Vander Veer[8] stated in their original paper, "Immunizing injections with the pollen of one grass gives clinical relief of symptoms in those cases that have reacted to all (the grasses)." More recently, Cooke[9] has reaffirmed his belief that treatment with an extract of timothy alone is effective for all of the grass cases.

In contrast to these observations, Watson and Kibler[10] found that of their patients sensitive to Bermuda grass, a large percentage had no skin sensitivity to timothy and thus question the advisability of the use of timothy pollen extract in their patients. Lamson and Miller[11] and Lamson and Alles[12] also confirm the lack of complete multiple sensitivity in their grass-sensitive patients and conclude that the reactive substances in pollen are specific. Henderson[13] states that several patients who failed to be relieved by treatment with timothy extract alone often became improved after treatment with a mixed grass pollen extract. Similarly, Anderson[14] advocates the use of mixed extracts, contending that if some pollens are left out of the treatment mixture, the patient may have hay fever on exposure to these pollens.

With the discovery by Prausnitz and Küstner[15] of the principle of local passive transfer of sensitiveness to the skin of normal individuals and confirmation of this in the matter of transfer of hay fever sensitivity by DeBesche,[16] the way was found for the investigation of the interrelationship of pollens. In 1925 Coca and Grove[17] made use of the passive transfer method and published the result of an experiment in which passively sensitized sites were desensitized by one antigen and were later tested with another antigen. In two cases this second pollen antigen caused a reaction in the site which had been desensitized to the first antigen. Also, a second method of studying the interreaction of sensitive serum and pollen was outlined by these same authors. Mixtures of atopic (sensitive) serum and atopen (pollen) were made

in vitro and used to prepare sites in normal persons. It was found that the addition of atopen had neutralized the reagin (antibody) in the serum so that on the next day the injection of pollen extract in the same place failed to cause a reaction. This neutralization has been studied in greater detail by Levine and Coca.[18] More recently Harley[19] has made an extensive study of the method and has presented an interesting schematic outline of the immunologic principles involved.

Coca and Grove,[17] using the method of active desensitization in a limited number of cases and using four different grass pollen extracts, came to the conclusion that since timothy reacted in a desensitized orchard grass site, and since orchard grass did not react in a desensitized timothy site, that some of the atopens contained in timothy were lacking in orchard grass.

In similar fashion Chobot[20] showed that timothy pollen extract desensitized against Bermuda grass and vice versa. In a small group of hay fever patients, he noted that the skin sensitivity to these two grasses was equal in incidence and in degree.

Piness and Miller,[21] on the other hand, testing 599 patients with ten different grasses, found 107 single reactions. By the method of testing desensitized skin sites, they found that their results varied according to the serum used for the local passive sensitization of these sites. The serum was an important variable.

Stull, Cooke, and Barnard[22] were unable to confirm these results of Piness and Miller. Using eleven sensitive serums and seven different grasses, they found that each grass pollen desensitized against all the others, and on the basis of these findings as well as of their fourteen years of clinical experience in treating with timothy pollen extract alone, they concluded that the active principle in all grass pollens is single and the same.

Investigation of the chemistry of pollen extracts by Cooke,[23] by Caulfeild,[24] by Bernton,[25] and by the Moores,[26] and their several coworkers, have been concerned chiefly with the identification of the active principle in the extract and with the question of whether this principle is single or multiple. Most of this work has been done with ragweed pollen. It is of little assistance to this present study.

Our own observations of patients in the clinic indicate that whereas most of our patients with early hay fever show positive skin reactions to all of the grass pollens at the same time and in about the same degree, there are occasional instances of a single sensitivity and other instances of reactions to only two of several grasses. A more common variation noted is that of different degrees of skin reaction to the different grass pollen extracts in a given individual. Furthermore, our results of treatment with a single grass pollen extract have not been as satisfactory as the results in other cases in which at least two pollen extracts were used.

The great divergence of observation and conclusion discussed in the foregoing indicates all too clearly that the whole question of the biologic specificity of the grass pollen extracts is still an open one.

In order to study it further and perhaps thereby to improve our own technic and results, it was decided to study the active desensitization of passively sensitized skin sites and the crossed reactions obtained by the common New England pollens. Further, we elected to utilize, as recipients for the passive sensitization of local skin sites, allergic patients who were non-sensitive to pollens. We chose the method of local desensitization in situ, first, because we anticipated a later study of desensitization of actively sensitized sites and, second, because we wished to avoid any other additional variation that the preliminary incubation of the antigen and serums might introduce.

EXPERIMENTAL

The serums in all cases were secured from patients who were highly sensitive to the grasses and, if possible, to other unrelated substances at the same time. It was important that the blood should contain reagins to a variety of antigens. After being drawn, the blood was allowed to clot overnight in the refrigerator and the serum was separated the following morning. No preservative was added. Cultures for sterility and Hinton tests for syphilis were negative in each serum used.

The recipients who were selected for the passive transfer tests included 47 patients with asthma, 10 with perennial vasomotor rhinitis, and 1 with angioneurotic edema. Each of these prospective recipients was first tested on one arm by an intracutaneous injection of the various pollen extracts to be studied. If these were negative, then a series of intracutaneous injections of sensitive serums of exactly 0.1 c.c. each were made on the lateral aspect of the opposite arm. These were arranged in a single row with at least 1½ inches between the adjacent sites. The sites were marked, and on the next day and subsequent days these passively sensitized sites were desensitized by a series of intracutaneous injections of the particular pollen extract, great care being exercised to carry out such injections always through the same skin puncture and in the same direction as the initial injection of serum. Figure 1 shows the exact method of desensitization. It represents a typical result obtained in one of the recipients. In this case, the sites were easily desensitized by three daily injections of red top pollen extract and then were found to be also desensitized both to orchard grass and to timothy extracts, whereas, in spite of the preliminary treatment, ragweed still reacted well. In each experiment it was demonstrated beforehand that the sensitive serum used had reagins for all the various antigens to be used. The positive ragweed reaction demonstrates that the desensitization is a specific phenomenon

and not merely a nonspecific exhaustion. All readings were made in about twenty minutes after the time of injection of extract or serum.

By this method desensitization with the pollen extracts of timothy, orchard grass, red top, sweet vernal, plantain, and short ragweed, and the interrelationship of the different pollen extracts were studied, each in a different series of patients. The gross results are shown in Table I.

The entire study involved the use of 21 different serums and a total of 58 different recipients. Thus, 18 sites were desensitized to orchard

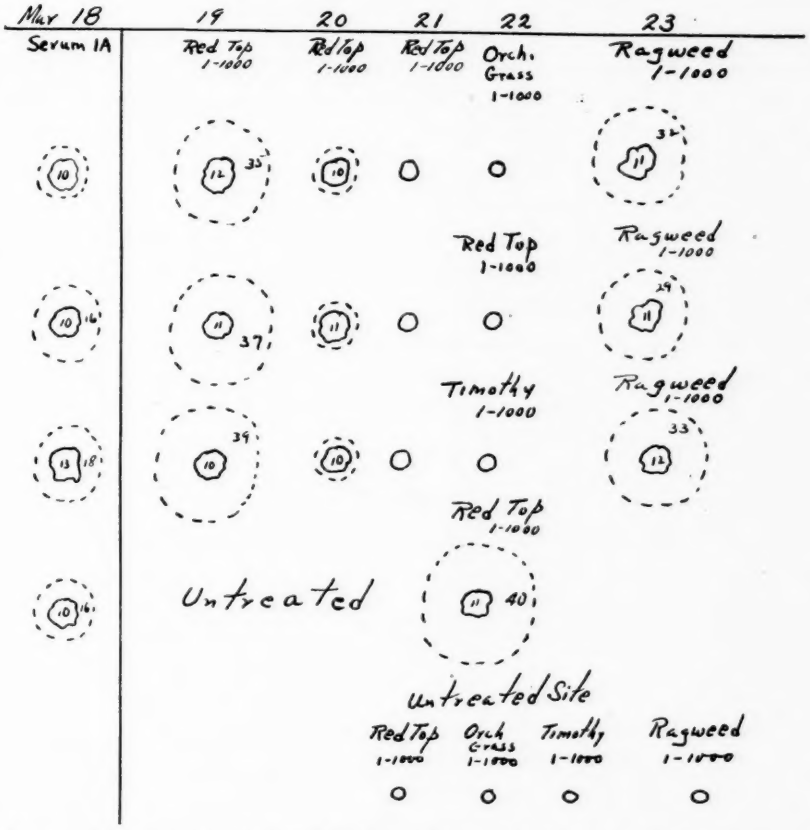

Fig. 1.—Technic of local desensitization. Serum 1A, recipient No. 14. Figures in small circles are the diameters of wheal in millimeters. Figures in large circles are the diameters of erythema in millimeters.

grass and were then tested with timothy, but only 2 reacted. According to these results summarized in Table I, there is a close antigenic relationship between the pollens of timothy, red top and orchard grass. In most instances, desensitization of a passively sensitized site with one of these grass pollens resulted in a desensitization to the other two grass pollens at the same time. No such relationship, however, is shown between these particular grasses and sweet vernal grass or plantain or ragweed. This detail fits well with clinical experience that patients

TABLE I

CROSSED REACTIONS TO GRASS POLLENS IN PASSIVELY SENSITIZED SKIN SITES

DESENSITIZED TO	TIMOTHY	ORCHARD GRASS	RED TOP	SWEET VERNAL	PLANTAIN	RAGWEED
Timothy	—	19—5	19—3	3—2	3—1	14—14
Orchard grass	18—2	—	20—1	1—1	4—0	15—15
Red top	21—4	21—4	—	3—3	3—0	13—13
Sweet vernal	7—6	7—7	7—6	—	7—0	6— 6
Plantain	7—7	5—5	5—5	4—4	—	3— 3
Ragweed	5—5	5—5	4—4	4—4	4—0	—

First figure = number of desensitized sites tested with another pollen extract.
Second figure = number of crossed reactions obtained.

skin sensitive to grasses and plantain are successfully treated by the former but not by the latter. Evidently, plantain does not have a factor present in grasses. It is interesting that ragweed desensitizes sites so that plantain no longer reacts. The complete lack of relationship between the grasses and ragweed is striking.

The tree pollens were investigated by similar methods. Birch, oak, maple, and willow were used for a study of crossed reactions in a group of five different serums from patients giving large reactions to all the tree pollens and a group of thirty-five different recipients. Figure 2 illustrates a typical case in which passively sensitized skin sites desensitized with oak pollen extract were also desensitized to maple but, nevertheless, remained sensitive to birch.

TABLE II

RELATIONSHIP OF CROSSED REACTIONS TO TREE POLLENS IN PASSIVELY SENSITIZED SKIN SITES

	BIRCH	OAK	MAPLE	WILLOW
Birch	—	11—1	9—0	5—0
Oak	12—12	—	8—2	4—1
Maple	10—10	10—5	—	4—4
Willow	12—11	10—5	6—1	—
Ash	2— 2	—	—	—

First figure = number of desensitized sites tested with another pollen extract.
Second figure = number of crossed reactions obtained.

Table II gives a summary of the total results. Sites desensitized to birch remain nonreactive to oak, maple, and willow. None of the common tree pollens, however, will desensitize to birch. There is some crossed relationship between oak and maple in less than half the cases, but willow is even less efficient. It is interesting to observe that, when our hay fever patients whose symptoms begin in April and May are treated with birch, the results are usually satisfactory, and incidentally, birch pollen causes the largest skin reaction in most of them.

Meantime, a detailed study of the relationship between the three grasses common to New England—timothy, orchard grass, and red top —was in progress, and the results appear in Table III.

An examination of Table III reveals, as stated above, that in the majority of cases, timothy, orchard grass, and red top will each desensitize against the others and that this ability is relatively the same with each grass. Sites desensitized with timothy reacted to other grasses in a total of only 5 out of 19 instances; with orchard grass, other grasses "came through" in only 2 of 18 instances; while with red top, only 4 of 21 cases reacted to other grasses. Expressed in other terms, treatment with timothy desensitized to other grasses in 74 per cent of the cases; orchard grass in 89 per cent; and red top in 81 per

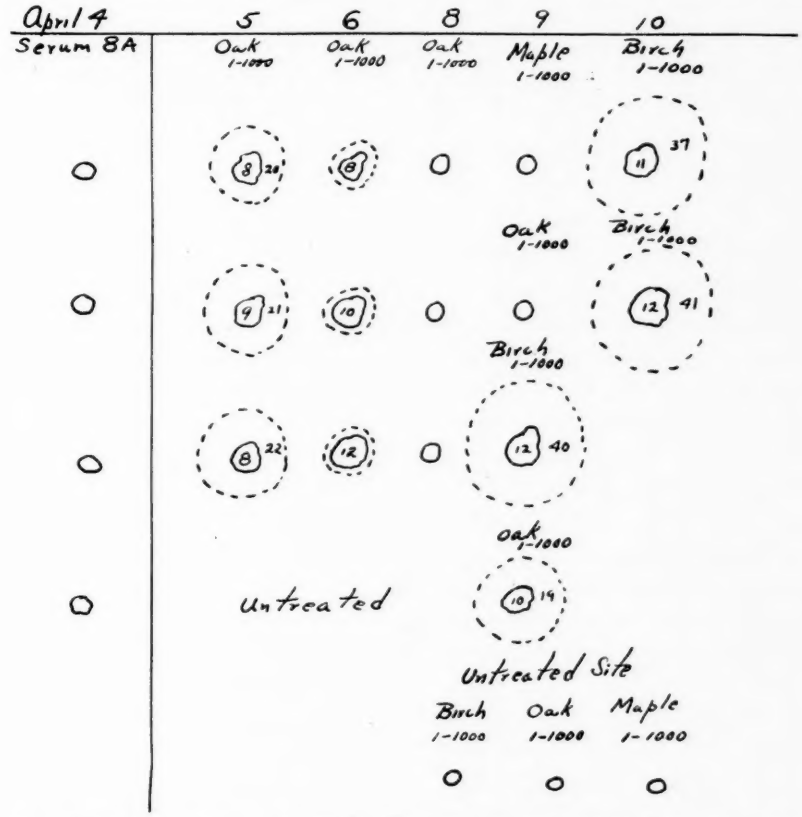

Fig. 2.—Technic of local desensitization. Serum 8A, recipient No. 20. Figures in small circles are the diameters of wheals in millimeters. Figures in large circles are the diameters of erythema in millimeters.

cent. It should be emphasized that in each instance the donor of the serum was skin sensitive to all of the grasses and his serum was capable of transferring this sensitiveness to a nonreactive recipient. These results do not confirm the conclusion of Coca and Grove[17] that timothy contains all the atopens and that orchard grass lacks some of them. Some of the experiments duplicate Coca and Grove's results. Others do not. The results suggest, however, that each grass pollen has certain atopens peculiar to itself and certain other atopens common to the other grasses.

TABLE III

CROSSED REACTIONS TO GRASS POLLENS IN PASSIVELY SENSITIZED SKIN SITES

SERUM USED FOR TRANSFERS	RECIPIENT TOTAL NUMBERS	SITES* DESENSITIZED WITH TIMOTHY	REACTED TO OTHER GRASSES	SITES* DESENSITIZED WITH ORCHARD GRASS	REACTED TO OTHER GRASSES	SITES* DESENSITIZED WITH RED TOP	REACTED TO OTHER GRASSES
1 A	14	5	0	5	1	4	1
3 A	6	2	2	1	0	3	1
5 A	8	3	2	2	0	3	0
11 A & B	4	0	0	1	1	3	1
12 A	2	1	0	0	0	1	0
14 A	3	1	0	1	0	1	0
17 A	3	0	0	3	0	0	0
22 A	4	1	0	1	0	2	1
28 A	6	2	1	2	0	2	0
30 A	4	4	0	0	0	0	0
31 A	4	0	0	2	0	2	0
11	58	19	5	18	2	21	4

*The figure refer to the number of recipients used.

It occurred to us, however, that the variation in results might depend partly upon the qualities of the particular sensitizing serum but that in addition the recipient and his own particular reaction to the sensitizing and desensitizing process might be another variable factor. As stated above, most of the recipients were patients found in the allergy clinic but were carefully selected as being non-sensitive to pollens with negative pollen histories and with negative pollen skin tests. Consequently, the eleven experiments in which one grass failed to desensitize to other grasses were repeated, and for this several normal nonallergic recipients were used. Eight of the eleven negative recipients were retested with other serums and in three instances with dilutions of the serum first used, while other recipients were retested with the serums giving the higher incidence of negative results. Table IV shows the results. It is important to note what Table IV indicates: that each recipient was used in more than one experiment; that at least two serums were tested on him; and finally the observation, that in each case the results following one serum, whether positive or negative, were duplicated by the next serum. The behavior of each recipient was uniform and constant. Table IV indicates clearly that, regardless of the serum used, the recipient himself is an important factor in the desensitization of the passively sensitized spot. If some of the data in Table IV are rearranged according to the sensitizing serum used, it becomes obvious (Table V) that even when the same serum is used to produce passively sensitized sites in a number of different recipients, the subsequent desensitization of those sites will vary in accordance with the recipient.

The factor in the recipient is difficult to evaluate. Crossed reactions between major plant groups—trees, grasses and ragweed—do not oc-

cur. Treatment with one does not desensitize to another, any more than ragweed hay fever can be relieved clinically by grass treatment.

Within a group of closely related substances, however, crossed reactions do occur irregularly, and apparently they depend in some part upon some factor or factors in the particular recipient used. Since

TABLE IV

THE FUNCTION OF THE RECIPIENT IN CROSSED REACTIONS FOUND IN PASSIVELY SENSITIZED SKIN SITES

RECIPIENT	SERUM	SITES DESENSITIZED WITH	RETEST WITH		
			TIMOTHY	ORCHARD GRASS	RED TOP
1	1 A	Orchard grass	+	–	+
	11 B	Orchard grass	+	–	+
	1— 4 11 B	Orchard grass	+	–	+
	1—10 11 B	Orchard grass	+	–	+
11	5 A	Orchard grass	0	–	0
	22 A	Orchard grass	0	–	0
45	11 A	Orchard grass	+	–	0
	1—4 11 B	Orchard grass	+	–	0
	26 A	Orchard grass	+	–	+
14	1 A	Red top	0	0	–
	22 A	Red top	0	0	–
15	1 A	Red top	+	+	–
	1—2 11 B	Red top	+	+	–
	1—4 11 B	Red top	+	+	–
17	3 A	Red top	+	+	–
	22 A	Red top	+	+	–
18	3 A	Red top	0	0	–
	11 A	Red top	0	0	–
20	3 A	Red top	0	0	–
	12 A	Red top	0	0	–
25	11 A	Red top	+	+	–
	12 A	Red top	+	+	–
54	22 A	Red top	+	+	–
	31 A	Red top	+	+	–
29	1 A	Timothy	–	0	0
	11 B	Timothy	–	0	0
30	1 A	Timothy	–	0	0
	12 A	Timothy	–	0	0
33	3 A	Timothy	–	+	+
	14 A	Timothy	–	+	+
36	5 A	Timothy	–	0	0
	30 A	Timothy	–	0	0

in this study the recipients used were found in the allergy clinic and suffered from asthma, vasomotor rhinitis, and the like, it is proper to consider that the unknown factor was concerned with their allergic symptoms. For example, the lack of crossed protection and the subsequent reaction to another grass might depend upon an active sensitiveness which is latent in the recipient though not marked enough to produce a skin test.

If we consider that each pollen has a specific factor and a common factor and that the sensitive serum carries both to the recipient's test-

site, it may be that in most instances the desensitizing extract removes both factors at once, but that in certain cases the recipient is himself actively sensitive to the specific pollen factor. The results shown in Tables IV and V lend strong support to such a theory. Recipients numbered 11, 14, 18, 20, 29, 30, and 36 are desensitized by one grass and then remain desensitized to the other two grasses, and always to both of the other two. They have no inherent active sensitiveness. On the other hand, recipients numbered 1, 15, 17, 25, 45, 33, and 54 can be desensitized to one grass, but then retain a sensitiveness to both of the other two grasses. Is it possible that they are actively sensitive to the species-specific factor and could we say that desensitization with one extract removes the sensitiveness to the common factor and to that particular species-specific factor but it leaves the other species-specific factors in place? The question is hard to answer. In addition to the grass variation among recipients described in the foregoing, there are a number of other and minor observations which emphasize the variations.

TABLE V

DEMONSTRATION THAT CROSSED REACTIONS DEPEND UPON THE RECIPIENT AND NOT UPON THE SERUM USED FOR TRANSFER

SERUM	RECIPIENT	SITES DESENSITIZED WITH	RETEST WITH		
			TIMOTHY	ORCHARD GRASS	RED TOP
1 A	1	Orchard grass	+	−	+
	14	Red top	0	0	−
	15	Red top	+	+	−
	29	Timothy	−	0	0
	30	Timothy	−	0	0
3 A	17	Red top	+	+	−
	18	Red top	0	0	−
	20	Red top	0	0	−
	33	Timothy	−	+	+
	34	Timothy	−	+	+
11 A	18	Red top	0	0	−
	25	Red top	+	+	−
	45	Orchard grass	+	−	0
11 B	1	Orchard grass	+	−	+
	15	Red top	+	+	−
	29	Timothy	−	0	0
	34	Timothy	−	+	+
12 A	20	Red top	0	0	−
	25	Red top	+	+	−
	30	Timothy	−	0	0
22 A	11	Orchard grass	0	−	0
	14	Red top	0	0	−
	17	Red top	+	+	−
	54	Red top	+	+	−

The variable speed and ease with which the passively sensitized skin sites were desensitized is one of these. Of the total of 151 passively sensitized sites observed in the study, 32 were desensitized by the initial injection of extract, 49 by the second, 65 by the third, 3 by the fourth, and 2 by the fifth. There was no suggestive association of the desen-

sitization time with any of the pollens or serums used. The majority (76 per cent) were desensitized with two or three injections and the shorter and longer desensitization times occurred with all sera and all pollens. For example, serum 3 A produced spots in four different individuals who were desensitized with one, two, three, and four injections, respectively. Evidently, the time of desensitization depends upon some factor in the recipient.

Reactions to the original dose of sensitive serum varied in different recipients. They were more frequently observed with the older serums. They consisted of reddish swelling from 10 to 20 mm. in diameter, sharply defined, a sort of atypical wheal which appeared within an hour and lasted several hours. No one serum invariably produced these reactions, and their occurrence bore no relation to any subsequent reaction to pollen. They depended not upon the serum itself but upon some peculiar quality of the skin tests of the individual injected. One person in particular showed reactions to each of several serums injected. As shown by Foshay,[27] this phenomenon occurs more often with immune than with normal serum. Further study of this is in progress.

Peculiar flare reactions were observed during this investigation in 22 instances out of 151 passive transfer tests. It did not follow the dose of serum but was observed after the initial desensitizing dose and occurred usually from six to eight hours after the injection. It arose from the site of the immediate wheal and spread over two or three times the area as a dull erythema, reaching its maximum size in one to two hours. It lasted from four to eight hours. Similar observations were made during the course of other studies with the various carbohydrates of pneumococci. One of the authors developed a delayed flare following an intracutaneous injection of 0.1 c.c. of 1:1,000 solution of Type I pneumococcus carbohydrate in his own arm. Its time of appearance and development was quite similar to those described above.

In three instances there was swelling and tenderness that involved the major portion of the outer aspect of the arm to make a reaction comparable to those often observed in the treatment of hay fever. In these cases the reaction persisted for over twenty-four hours. Obviously, the severity of reaction precluded giving the second injection on the following day. When, however, it was given, no further reaction was obtained. In these particular recipients the same severe reaction resulted even when different serums were used for the original passive sensitization, and in one case the reaction with tree-sensitive serum was as bad as the reaction with grass serum. In another of the recipients a passive transfer test made later with kapok-sensitive serum also resulted in the same type of reaction. The association with the serum was investigated by mixing the serum with different extracts

in vitro and then using the mixture for the sensitization of new skin sites in five other recipients for each mixture. In no one of the five cases was a similar reaction obtained. It is clear that the abnormal response is due to some peculiarity in the skin tissues of the recipients and not to the allergen or to the sensitizing serums.

Nonreceptive recipients have been described by Coca and Grove,[17] but not once was one encountered in the seventy-five allergic subjects used for this study. This observation adds confirmation to the findings of Levine and Coca[18] and of Smyth and Bain[28] that individuals nonreceptive with one serum become receptive if a more sensitive serum is used. The same reasoning is good evidence of the fact that all serums employed in this study were of high sensitizing power.

The development of a general skin sensitiveness was observed in three other recipients not included in the above series. Whereas control tests with pollen extracts at the beginning and at the end of the first series were entirely negative, later a positive skin test could be elicited. In two of the three, however, this positive test was only to the particular pollen extract used in desensitization. Retesting of the individuals forty days later gave negative tests. The sensitivity was temporary. The observation indicates that at least a temporary general sensitization can be produced by repeated intracutaneous injections of a pollen extract, just as Simon and Rackemann[29] found that a general sensitiveness could be caused by repeated intracutaneous injections of a foreign serum. Lamson and Miller[30] treated thirty-three allergic individuals with pollen extracts in spite of the fact that they had no skin sensitivity. Doses of the same amount and frequency were used as in the treatment of sensitive individuals. The treatment was given subcutaneously, and the authors noted that no general sensitivity was induced by it. The relative infrequency of inducing sensitivity in this study suggests that the individual who becomes generally skin sensitive to pollens must possess some latent capacity not yet understood.

In two other recipients general sensitivity was observed to develop during the first test. The preliminary skin tests were negative, and the final ones were positive. That this conceivably occurred during and because of the test is strongly suggested in the subsequent follow-up of these individuals. They were retested at intervals of thirty days, and all tests after the first one were negative. Both recipients were asthmatics who gave a history of aggravation of symptoms during the hay fever season. Two weeks before the season, the skin tests were still negative. Three weeks later, when their asthma was definitely worse, the skin reactions were positive. These cases are apparently similar to those referred to by Caulfeild and his associates[24] and others. They give negative skin reactions in the off seasons and develop positive tests when exposed to a sufficient amount of pollen. In this connection, it is interesting to note in our cases that approximately

1.5 c.c. of the 1:1,000 extract intracutaneously given in small daily doses was sufficient to induce or bring out the general skin sensitivity. No symptoms were noted at the time of the injections, but the patients reported that various degrees of wheezing occurred during the following afternoon and evening.

DISCUSSION

These experiments do not help very much in the problem of selecting the particular pollen or pollens to be used in the treatment of hay fever. As the tables indicate plainly, crossed reactions between the different grasses and between the different trees are by no means unusual. Treatment of a passively sensitized site with either timothy, orchard grass or red top results in most instances in a simultaneous desensitization to the other two grasses. The cases are not numerous enough to give figures of sufficient size so that any close comparison can be made, but the important fact is that no one of the three grasses always and invariably produces a desensitization to the two others. In the case of the tree pollen the results have a greater practical value because, whereas birch desensitizes to oak, maple, and willow in most instances, none of these others desensitize to birch. The experiments indicate that birch should be used in the treatment of all patients with tree hay fever, and our clinical experience has been that birch does give results which are fairly satisfactory.

With the methods and technic employed here, variations are the rule, and ample evidence is presented to show that they depend in large part upon the particular recipient used as a test subject.

In these experiments most of the recipients were patients found in the allergy clinic. Even though they showed no evidence of pollen sensitiveness, many of them were "allergic individuals," and this fact may have altered the results. In another experiment with another group of allergens, it is planned to use as recipients only those individuals who have no trace whatever of allergic constitution or disease. The results may be different. However, there is increasing evidence that the differences between allergic individuals and normal individuals are more apparent than real.

Other variations among these particular recipients are also interesting though their significance is unknown. Reactions to the primary dose of sensitizing serum, flares following the first treatment of the passively sensitized site, and finally the development in a few cases of sensitiveness of the entire skin are interesting phenomena not to be explained by the evidence so far at hand. It is important to point out that in experiments depending on the passive transfer of sensitive serums from allergic individuals, the function of the recipient is an important variable which must not be overlooked. Whether some other method of investigating this problem will lead to different conclusions is a question for the future.

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PROTEIN CONTENT OF HUMAN SERUMS*

Analyses of Serums Before and After Pollen Injections

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INTRODUCTION

THIS paper is part of a chemical and serologic study of the mechanism of reaction and of protection in a certain type of allergy.

It has been shown that there is an increase in the globulin content of serum under various immunologic procedures and a review of the literature on these points is given by Wells.[1] Smyth and Bain[2] showed that the allergic skin-sensitizing substance was associated with the globulin fraction of serum. The small amounts of serum available made complete separation of the globulins impossible, but their results indicated that the euglobulin was inert and that the sensitizing substance was associated with the pseudoglobulin. After work with larger amounts of serum in this department,[3] the globulins were separated. The euglobulin was inert and the skin-sensitizing substance was associated only with the pseudoglobulin.

A report of work already published from this department[4] has shown that the amount of skin-sensitizing antibody in antetreatment and posttreatment serums was not materially affected by the therapeutic injection of a specific pollen extract. This indicated that there was no change in the amount of sensitizing substance, the pseudoglobulin. However, passive transfer sites when made with mixtures of posttreatment serum and pollen extract and tested after forty-eight hours with pollen extract required from four to ten or even twenty times the strength of pollen extract to give neutral sites as required by mixtures of antetreatment serum and pollen extract. This indicated that pollen injections might have caused an increase in the skin-sensitizing substance, namely pseudoglobulin.

The protein analyses on the serums here reported were carried out to determine whether treatment with pollen extract in pollen-sensitive cases caused any significant quantitative change in the serum proteins.

EXPERIMENTAL

The nineteen serums were taken before seasonal treatment from patients with positive histories of clinical hay fever. Seventeen patients had had no previous treatment by pollen injection, and two had been

*From the Department of Allergy of The Roosevelt Hospital, New York.

TABLE I

THE PROTEIN CONTENT OF HUMAN BLOOD. ANALYSES OF SERUMS TAKEN BEFORE (A) AND AFTER (P) POLLEN EXTRACT INJECTIONS AND OF NORMAL SERUMS

			GRAMS NITROGEN PER 100 C.C. OF SERUM								
CASE	SEX	SERUM	TOTAL	NON-PROTEIN	EUGLOB.	PSEUDOGLOB. 1	PSEUDOGLOB. 2	TOTAL GLOB.	ALBUMIN	ALBUMIN-GLOB. RATIO SERUM A	ALBUMIN-GLOB. RATIO SERUM P
Allergic Serums											
L. Hz.	M	A	1.346	0.157	0.131	0.210	0.087	0.428	0.761	1.8	
		P	1.403	0.131	0.127	0.220	0.077	0.424	0.848		2.0
P. Gn.	M	A	1.318	0.170	0.112	0.230	0.084	0.426	0.722	1.7	
		P	1.287	0.131	0.050	0.249	0.066	0.365	0.791		2.2
E. Sn.	M	A	1.283	0.140	0.073	0.166	0.074	0.313	0.830	2.6	
		P	1.297	0.136	0.082	0.169	0.084	0.335	0.826		2.5
L. Sr.	M	A	1.332	0.183	0.130	0.179	0.070	0.379	0.770	2.0	
		P	1.365	0.130	0.115	0.165	0.091	0.371	0.864		2.3
J. Kr.	M	A	1.424	0.131	0.191	0.219	0.074	0.484	0.809	1.7	
		P	1.362	0.108	0.130	0.256	0.082	0.468	0.786		1.7
S. Km.	M	A	1.494	0.140	0.148	0.210	0.026	0.384	0.970	2.5	
		P	1.337	0.108	0.096	0.195	0.091	0.382	0.847		2.2
J. Sl.	M	A	1.276	0.109	0.144	0.144	0.110	0.398	0.769	1.9	
		P	1.295	0.104	0.119	0.134	0.148	0.401	0.790		1.9
L. Ge.	M	A	1.339	0.118	0.124	0.214	0.083	0.421	0.800	1.9	
		P	1.362	0.087	0.112	0.117	0.152	0.381	0.894		2.3
J. Sr.	M	A	1.382	0.131	0.106	0.100	0.131	0.337	0.914	2.7	
		P	1.316	0.260	0.136	0.078	0.121	0.335	0.721		2.2
R. Ln.*	M	A	1.368	0.136	0.052	0.232	0.114	0.398	0.835	2.1	
		P	1.336	0.157	0.068	0.193	0.087	0.348	0.831		2.4
B. Cs.	F	A	1.325	0.140	0.141	0.231	0.075	0.447	0.738	1.6	
		P	1.304	0.136	0.124	0.214	0.074	0.412	0.756		1.8
M. Ma.	F	A	1.311	0.127	0.070	0.306	0.100	0.476	0.708	1.5	
		P	1.456	0.131	0.062	0.323	0.136	0.521	0.804		1.5
I. Pt.	F	A	1.322	0.131	0.094	0.183	0.106	0.383	0.808	2.1	
		P	1.393	0.139	0.195	0.182	0.100	0.477	0.777		1.6
R. Kn.	F	A	1.311	0.069	0.122	0.193	0.118	0.433	0.808	1.9	
		P	1.498	0.104	0.144	0.226	0.104	0.474	0.920		1.9
G. Wh.	F	A	1.269	0.109	0.168	0.179	0.083	0.430	0.730	1.7	
		P	1.274	0.131	0.128	0.148	0.121	0.397	0.747		1.9
A. Kn.	F	A	1.479	0.096	0.190	0.192	0.083	0.465	0.918	1.9	
		P	1.326	0.095	0.111	0.113	0.195	0.419	0.812		1.9
E. Hn.	F	A	1.297	0.122	0.165	0.197	0.078	0.440	0.735	1.7	
		P	1.208	0.087	0.080	0.173	0.130	0.383	0.738		1.9
K. Gd.*	F	A	1.357	0.126	0.050	0.258	0.131	0.439	0.791	1.8	
		P	1.262	0.144	0.064	0.228	0.092	0.384	0.734		1.9
R. St.	F	A	1.276	0.131	0.122	0.206	0.087	0.415	0.730	1.8	
		P	1.246	0.122	0.144	0.182	0.095	0.421	0.703		1.7
Normal Serums											
J. Bd.	M	1†	1.375	0.135	0.103	0.214	0.070	0.387	0.853	2.2	
		2†	1.325	0.148	0.110	0.206	0.082	0.398	0.779	2.0	
M. Gn.	F	1†	1.265	0.144	0.059	0.192	0.092	0.343	0.778	2.3	
		2†	1.339	0.149	0.106	0.149	0.083	0.338	0.852	2.5	
M. Jn.	F	1†	1.254	0.131	0.074	0.087	0.184	0.345	0.778	2.2	
		2†	1.424	0.153	0.165	0.219	0.113	0.497	0.774	1.5	

*Treated in previous season.

†Serum samples taken during the same season and interval as the A and P serum.

treated in the previous year. These patients all gave positive skin reactions to intradermal tests with pollen extracts. They were treated by subcutaneous injection with increasing protein unit[5] dosage of pollen extract at weekly intervals for approximately twelve weeks when the serum was again taken. The serums taken before treatment were designated "Serums A" and those taken following treatment "Serums P."

The normal serums were taken from individuals with no familial or personal histories of allergy and giving no reaction to an intradermal test injection of 0.025 c.c. of pollen extract 1,000 units[5] per cubic centimeter. Serums were taken at intervals of about twelve weeks and were analyzed during the same season and interval as the serums from the pollen-treated cases under study.

The blood was drawn in 30 to 40 c.c. amounts and was allowed to clot. The serum was separated, Seitz filtered and preserved sterilely at 7° C. Analyses were made within two months following the taking of the blood.

The protein analyses were carried out by the fractional sodium sulphate precipitation method of Howe.[6] Duplicate Kjeldahl analyses were used in the calculation of the nitrogen content, and results are expressed as grams of nitrogen per 100 c.c. of serum (Table I).

TABLE II

THE PSEUDOGLOBULIN CONTENT OF ALLERGIC SERUMS TAKEN BEFORE (A) AND AFTER (P) POLLEN EXTRACT INJECTION

CASE	SEX	POLLEN EXTRACT	TOTAL DOSAGE UNITS	TOTAL PSEUDOGLOBULIN GRAMS N 100 C.C. SERUM		PSEUDOGLOBULIN PROTEIN RATIO	
				SERUM A	SERUM P	SERUM A	SERUM P
L. Hz.	M	Ragweed	169,800	0.297	0.297	0.25	0.23
P. Gn.	M	Ragweed	43,170	0.314	0.315	0.27	0.27
E. Sn.	M	Ragweed	249,970	0.240	0.253	0.21	0.22
L. Sr.	M	Ragweed	165,770	0.249	0.256	0.22	0.21
J. Kr.	M	Ragweed	73,170	0.293	0.338	0.23	0.27
S. Kn.	M	Ragweed	179,620	0.236	0.286	0.17	0.23
J. Se.	M	Ragweed	10,310	0.254	0.282	0.22	0.24
L. Ge.	M	Ragweed	47,790	0.297	0.269	0.24	0.21
J. Sr.	M	Ragweed	12,470	0.231	0.199	0.18	0.19
R. Ln.*	M	Ragweed	197,750	0.346	0.280	0.28	0.24
B. Cs.	F	Ragweed	47,320	0.306	0.288	0.26	0.25
M. Ma.	F	Ragweed	247,370	0.406	0.459	0.34	0.35
I. Pt.	F	Ragweed	102,710	0.289	0.282	0.24	0.22
R. Kn.	F	Ragweed	60,690	0.311	0.330	0.25	0.24
G. Wh.	F	Ragweed	47,450	0.262	0.269	0.23	0.24
A. Kn.	F	Ragweed	67,354	0.275	0.308	0.20	0.25
E. Hn.	F	Ragweed	30,220	0.275	0.303	0.23	0.27
K. Gd.*	F	Ragweed	28,470	0.389	0.320	0.32	0.29
R. St.	F	Timothy	48,360	0.293	0.277	0.26	0.25
Average				0.293	0.295	0.242	0.245
Average Normal Serums (Calculated from Table I)				0.282		0.236	

*Treated in previous season.

DISCUSSION OF RESULTS

The analyses in Table I show no significant variation in the serum proteins that can be attributed to the pollen treatment. The average albumin-globulin ratios of both antetreatment and posttreatment serums is 1.9 which is in close agreement with the average ratio of 2.1 on normal serums.

In Table II is given a comparison of the total pseudoglobulin and the pseudoglobulin-protein ratios in the Serums A and Serums P. The total pseudoglobulin varies no more in the serums before and after treatment than it does in the normal serums, and the average pseudoglobulins in these serums are alike. These patients were all treated with high dosage of pollen extract and in most instances had satisfactory clinical results.

SUMMARY

Protein analyses of nineteen human allergic serums taken before and after treatment with pollen extract showed no significant difference in the actual or relative amount of proteins.

Similar analyses of normal serums gave results in close agreement with these.

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CHEMICAL STANDARDIZATION OF POLLEN EXTRACTS*

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THE excitant of hay fever in pollens possesses two properties of protein; the first and more striking is its large molecular size (Grove and Coca,[1] 1925), and the second is its antigenic property, which is relatively weak (Walzer and Grove,[2] 1925). That these two properties are not sufficient to prove the pollen excitant to be a protein is seen in the fact that both of them are exhibited by toxins and by some enzymes, neither of which have been proved to be proteins. No other evidence demonstrating the protein nature of the pollen excitant is available, although other inconclusive parallels have been reported. There is also no evidence that it is not a protein.

The belief of those who advocate that the phosphotungstic acid-precipitable "protein" in the extracts could be identified as the pollen excitant was disproved a priori by Ella F. Grove's demonstration of the digestibility or dialyzability of nearly all of it without appreciable loss of specific activity; and later by the finding of one of us (Coca[3]), which has been confirmed by Spain and Newell,[4] that when phosphotungstic acid-precipitable protein has been separated from the pollen extract through a semipermeable membrane it is seen to be lacking in specific activity.†

The foregoing established facts would seem to discourage efforts to standardize pollen extracts by any chemical method involving a precipitation of the small-molecular specifically inert protein. Hubbard and Osgood[5, 6] have recently recommended that some allergenic extracts, including those of pollens, be standardized according to their content of trichloracetic acid-precipitable nitrogen. Those writers prefer this precipitant to the phosphotungstic acid used by Cooke and Stull[7] because of "its more highly specific nature," referring to the well-known fact that phosphotungstic acid precipitates not only native protein but also proteose, peptone, and even polypeptids.

In their first paper Hubbard and Osgood determined the protein content of a number of allergenic extracts with the two precipitants mentioned above, and in all instances they obtained lower values with trichloracetic acid. In the almond extract alone the trichloracetic acid figure (4.62) was only slightly lower than that obtained with phosphotungstic

*From the Lederle Laboratories.

†In one experiment Spain and Newell succeeded, even with a less suitable membrane (cellophane), in obtaining a wholly inactive filtrate which contained 11 per cent of the phosphotungstic acid-precipitable nitrogen of the original pollen extract.

acid (4.80), the explanation of this being, according to these writers, that "almost all of the P. T. A.-precipitable N. was in the form of true protein." They assume from their experiences that the chemical standardization of the usual allergenic extracts with phosphotungstic acid precipitation gives too high figures, whereas that with trichloracetic acid precipitation yields approximately correct results because all the true protein and nothing but the true protein is precipitated with trichloracetic acid.

Some unpublished experiments by one of us (Coca) with an extract of dried bean had yielded results which threw doubt upon these assumptions. W. W. Duke[8] had described a case of unusual sensitivity to bean; the serum from this patient possessed a high sensitizing power. He stated that he was unable with most drastic chemical treatment to destroy the specific activity of the bean extract, and on this account he actually considered the possibility that the bean excitant is not a protein.

Among some experiments which were undertaken to test this impression was included the following:

> To a strong undialyzed extract of dry bean were added some 10 per cent H_2SO_4 and successive quantities of a 10 per cent solution of phosphotungstic acid until no precipitation could be caused in the clear supernatant fluid by a further addition.
>
> The final phosphotungstic acid-negative supernatent contained not only considerable nitrogen but also specific excitant (skin tests*).

A reasonable interpretation of this result seemed to be that the precipitation of the protein excitant of the bean extract by phosphotungstic acid was partially inhibited by dialyzable, perhaps nonprotein, nitrogenous substances in the extract, and this idea has been substantiated in the following experiment.

Three pounds of ground, dry kidney beans were extracted for twelve hours with 3 liters of phosphate buffered saline solution. The paper and Seitz filtered extract contained 11.6 mg. N per c.c. Six hundred c.c. of this extract were dialyzed under toluol against daily changes of large quantities of extracting fluid. At intervals of about three days a 30 c.c. sample of this extract was taken from the dialyzing sac and placed in a small collodion dialyzing thimble in which it was dialyzed for twenty-four hours against 50 c.c. of extracting fluid; a Kjeldahl nitrogen determination was then made on this entire 50 c.c. dialysate. The nitrogen content of these sample dialysates diminished until the sixteenth day when it reached that of the blank test (0.014 mg. N per c.c.). At this

*These tests were made in the skin of a normal person (C. V.) passively sensitized with the strong serum, referred to above, which was obtained through the courtesy of Dr. Duke.

point the nitrogen content of the extract in the large dialyzing sac had dropped to 4.3, remaining constant thereafter. Dialysis was continued until the twenty-seventh day.

Through this procedure it could be seen that after the twenty-seven days' dialysis practically all dialyzable matter extracted from the beans had been eliminated.

Seventy-five c.c. of the thoroughly dialyzed bean extract were mixed with 5 c.c. of 10 per cent H_2SO_4 and 20 c.c. of 10 per cent phosphotungstic acid. In the clear supernatent (A) obtained by centrifugation no phosphotungstic acid precipitable substance remained, and duplicate 10 c.c. samples of the fluid, tested with the Kjeldahl method, were found to contain no nitrogen whatever. All the nondialyzable protein in the dialyzed extract was precipitable with phosphotungstic acid.

In order now to see whether the phosphotungstic acid precipitation of protein is inhibited by dialyzable extractives of the bean, the original, undialyzed extract was diluted to the same nitrogen content (4.3 mg. per c.c.) as that of the dialyzed extract; and it was found, first of all, that 7½ times as much of the 10 per cent phosphotungstic acid solution as was needed for the dialyzed extract had to be added before no further precipitation could be obtained in the supernatent. Furthermore, the clear supernatent (B) after thorough dialysis and concentration to about the original volume was found to contain a quantity of nondialyzable (protein) nitrogen, which was equivalent to about one-third of the protein content of the original undialyzed bean extract.

With these results in hand we were in position to examine the assumption of Osgood and Hubbard that the protein content of an allergenic extract can be more closely determined with trichloracetic acid precipitation than with phosphotungstic acid precipitation.

In the tests with trichloracetic acid we followed exactly the procedure described by Hubbard and Osgood,[5] including the one and one-half minute heating previous to the addition of methyl alcohol.

The dialyzed and also the undialyzed bean extract were treated with trichloracetic acid in such quantity that the supernatent showed no further precipitation upon addition of the reagent. In both instances, however, a further precipitation could be obtained by addition of a little 10 per cent phosphotungstic acid, which proves the superiority of the latter reagent over trichloracetic acid as a protein precipitant under the conditions of the experiment. It also reveals the fallacy of the general assumption of Hubbard and Osgood that trichloracetic acid is a "more specific" precipitant of protein than phosphotungstic acid.

In their second paper, Osgood and Hubbard (making use of the method of Katherine L. Bowman, by which the relative specific activity of two pollen extracts can be estimated within 20 per cent) have reached the conclusion that the chemical standardization of two pollen extracts is more accurately determined with trichloracetic acid precipitation than

with phosphotungstic acid precipitation or with the content of total nitrogen. One of the two extracts that they were comparing had been prepared by repeated (7 times) Seitz filtration, a treatment which is practically never used in the ordinary preparation of pollen extracts. The conclusions that are reached apply, therefore, only in this special case.

There are excellent reasons in the published experimental work on this subject for anticipating that standardization of pollen extracts with the method of trichloracetic acid precipitation, as described by Osgood and Hubbard, will be found inferior in accuracy and simplicity to the method of total nitrogen content, which has been found satisfactory by S. W. French,[9] by one of us (Coca[3]) and by Katherine L. Bowman.[10]

SUMMARY AND CONCLUSIONS

1. It has been shown that a vegetable extract (bean) may contain dialyzable substances which may greatly interfere with the precipitation of protein, by both phosphotungstic acid and trichloracetic acid.

2. Protein solutions free from inhibiting substances by dialysis may be completely precipitable with phosphotungstic acid but not completely precipitable with trichloracetic acid.

3. The trichloracetic acid precipitation method, as described by Osgood and Hubbard, has not been shown to be superior to the method of total nitrogen content in the chemical standardization of pollen extracts.

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STUDIES IN CONTACT DERMATITIS*†

I. Adhesive Plaster Dermatitis: Technics for Surface Testing on Patients Sensitive to Adhesive Plaster

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THE application of adhesive plaster to the skin occasionally produces irritation. In such instances this manifests itself, rarely in a few hours, but more frequently it develops after the plaster has been in contact with the skin for several days. The irritation varies in degree from a mild erythema to an intense dermatitis (type venenata) with destruction of the outer skin layers. The patient may complain of itching, burning, and pain at the affected site.

Aside from its therapeutic application, adhesive plaster forms a constituent part of the patch or surface test used in the diagnosis of contact dermatitis. In this technic the material to be tested is placed in contact with the skin and covered by a square of some impermeable membrane. Over this a larger square of adhesive is applied to hold the test material and its cover in place. Under these circumstances, any irritation of the skin which may be produced by the adhesive presents a distinct problem, in that it interferes with a correct reading of the test.

In making routine patch tests in cases of contact dermatitis, I encountered this difficulty quite frequently. A series of studies was thus begun in an effort to determine what factors were producing the irritation of the skin. For this work it was necessary to procure a technic for testing which avoided the use of adhesive plaster. The present communication will be devoted to a discussion of the development of several substitute procedures which were used in surface testing those individuals who gave evidence of adhesive plaster intolerance.

The term adhesive plaster dermatitis, as it has been generally referred to, is rather loosely employed, in that it is used to cover all forms and degrees of irritation from adhesive plaster. As a result of certain impressions gathered from my studies, I shall attempt to separate the different forms of adhesive dermatitis. I shall present my observations and views on this matter in a subsequent communication. For the present, however, it may be stated for the sake of clarity that adhesive plaster dermatitis may be of two types: (a)

*From the Department of Applied Immunology, Jewish Hospital.
†Read in part before the eighth annual meeting of the Society for the Study of Asthma and Allied Conditions, April 30, 1932.

specific dermatitis, in which the subject is found specifically sensitive by patch or surface test to one or more of the ingredients of adhesive plaster; and (b) nonspecific dermatitis, in which the subject does not react specifically to the ingredients comprising adhesive plaster but in which the irritation is brought about by mechanical or traumatic factors.

There have been several earlier investigations into the nature of adhesive dermatitis. Seeliger in 1926[1] believed that irritation of the skin due to adhesive plaster varied with the type of skin. He utilized five brands of adhesive plaster for testing and interpreted the cutaneous reactions according to such changes as faint redness, itching, eczema, and maceration. His subjects were divided into three groups: (1) those with white skin and blond hair, (2) those with slightly pigmented skin and medium blond hair, and (3) those with strongly pigmented skin and dark hair. Group one showed the greatest number of reacting persons, group two the next largest, and group three the least number. He found that the following specimens of adhesive produced the greatest irritation in the order listed, namely Germanioplast, Leukoplast, Rosaplast, Tutoplast, and Helfoplast. In testing other series of subjects he determined that skin toughened by exposure to sun and air was nonreactive. He concluded that cutaneous irritation of the skin by adhesive depended on the nature or constitution of the skin, and on the kind of adhesive plaster used. He believed Helfoplast* was the least irritating of adhesives because it was said to contain no resin acids, which, in his opinion, caused the undesirable reactions.

Siemens[2, 3] found that even Helfoplast might cause an erythema. He quoted Bloch to the effect that he had found 11 cases among 1,100 patients, most of them eczematous individuals, who were sensitive to Leukoplast (a resin-containing brand of adhesive plaster); also that among 800 normal persons three positive instances were detected. Thus Bloch believed that one in 150 to 200 of all types of skins were sensitive to adhesive plaster. Siemens, however, believed the incidence to be even higher. Mayer[4] found that Bonnaplast and Helfoplast caused the least number of skin irritations. Stauffer[5] stated that in his experience adhesive plasters which never gave irritation did not exist. In discussing the patch test he cautioned that the impermeable material which covers the test substance should not be irritating. He noted that adhesive plaster as an outer covering in the patch test had the disadvantage of frequently causing skin irritation of such a severe

*A communication from Germany as recently as 1932 indicated that Helfoplast was still considered a nonallergic adhesive plaster, even though it had a rubber content up to 32 per cent and resin up to 15 per cent. The manufacturers claimed that the resins were neutralized so that there was no free resinous acid to produce any reaction.

degree as to involve not only the cutaneous surface which it touched, but also that surface under the special material covering the application, thus making it impossible to obtain a reading.

In earlier studies by Siemens[2, 3, 6] and Unna[7] on the nature of adhesive dermatitis very little was mentioned of the routine technic employed in their investigations. The so-called patch test was originally employed by Jadassohn[8] as a "functioneller Prüfing der Haut" to determine the sensitivity of skin to specifically offending substances. The material to be tested was placed on the skin and retained in position by means of a piece of adhesive plaster. With but minor variations this procedure has been used up to the present time. Bloch[9] used a square of gutta-percha to separate the test material from the sticking plaster. For the same purpose Spain and Cooke[10] covered the blotting paper holding the test substance with a larger square of glazed paper. Ramirez and Eller[11] employed rubber tissue as the impermeable membrane, while Sulzberger and Wise[12] protected the test material by gutta-percha, oil silk, or other impervious tissue. Stauffer[5] made use of Mosetig-Batiste (a rubberized cloth made in Germany; it is treated probably with a vegetable oil), gutta-percha or cellophane. Mayer[4] preferred Billroth-Batiste (an oil treated rubberized cloth), gutta-percha, or cellophane; and Kesten and Laszlo[13] used cellophane or Silkoid. In common, however, all investigators employed adhesive plaster to fix the test substance and the impermeable membrane covering it to the skin.

Obviously none of these methods of testing were applicable in patients exhibiting reactivity to adhesive plaster. For this purpose Mayer[4] mentioned the use of gutta-percha or batiste which was sealed down at the edges with mastisol;* and, when this was unsatisfactory, he bandaged the test to an extremity. There is doubt, however, as to the advisability of using such a preparation as mastisol, which contains a high percentage of an oleoresin and is, furthermore, a proprietary preparation subject to changes in formula. Any substitute procedure which is offered for testing in these types of cases must be evaluated in the light of the possible irritating properties of the constituents contained in the shielding membrane, and in the fixing substance or adhesive.

In the routine patch or surface test, I had in the past been using cellophane underneath the adhesive plaster. To eliminate the latter, in the present investigation, it was necessary to employ some other substance to seal the cellophane to the skin. Flexible collodion (a mixture of collodion [95 per cent] with camphor [2 per cent] and castor oil [3 per cent]) was tried at the start in my first study, in

*Mastisol is used in Germany to fix dressings to the skin. It is made under the following formula: Mastix 20 grams; chloroform 50 grams; linseed oil 20 drops. Another formula substituted castor oil for the linseed oil. Still another used benzol instead of chloroform, and an ester instead of linseed oil.

association with M. Walzer.[14] The cellophane was cut into discs, a ring of collodion was stamped on the skin, and the discs were then applied and fixed to the skin by gentle pressure. We were impressed with the cleanliness and the comparative simplicity of the technic, and appreciated the possibilities of this procedure which, because of the transparency of the shielding membrane, permitted observation of the underlying test substance and skin.

Since cellophane is relatively new as an item of commerce, a brief statement concerning some of its properties would be in order. Cellophane is regenerated cellulose in sheet form, made from purified wood or cotton pulp by a chemical procedure known as the viscose process. The viscose solution is rolled under pressure into thin sheets of varying thicknesses, which, after further processing, are passed through a glycerol bath to maintain a soft flexible texture. They are then dried. Thicker sheets are made by plying together several thinner ones, with the aid of suitable gelatin or dextrin adhesives.

There are two forms of cellophane, the plain transparent and the moisture proof. The latter variety is highly transparent and lustrous, resulting from a surface coating which gives it moisture-proof qualities. Plain cellophane permits the rapid penetration of water vapor and of readily water soluble gases such as ammonia and carbon dioxide. Therefore it cannot be referred to as an impermeable membrane. Sparingly water soluble gases such as hydrogen diffuse through it very slowly. Moisture-proof cellophane is practically impervious to all gases.

In surface testing I tried discs made up of both kinds of cellophane in varying thicknesses and sizes. Weight 600 was found to be the most preferable for general use. Weights 300 and 450, being too thin, were difficult to handle and wrinkled too much. Discs made up of the 1,200 weight were found to be too inflexible, so that there was a tendency for their margins to cut into the skin. The most practical size for the disc proved to be about one or one and one-quarter inches in diameter. These larger sized discs were advantageous in that the test substance at the center could be kept free from contamination with the peripheral collodion ring. Furthermore, the larger discs wrinkled less during their fixation on the skin than did smaller discs.

It was thought at first that the moisture-proof cellophane would be more serviceable than the plain kind, because of its slightly firmer consistency, its moisture-retaining property, and its ability to adhere better. It was soon learned, however, that evaporation was but slightly retarded by its use. Furthermore, it was frequently noted that on removing the disc a glistening substance was found covering the skin within the collodion ring. Little attention was paid to this until a strong reaction was obtained with a blank moisture-proof disc

in a patient who was markedly sensitive to poison ivy and to adhesive plaster. This finding was later noted in two other instances. Its probable cause was the resin contained in the coating used for moisture proofing the cellophane.* This phenomenon will be discussed in greater detail in a subsequent paper. The common incidence of sensitivity to the coating of moisture-proof cellophane eliminated it from further consideration as a covering material for patch tests in cases of adhesive dermatitis. This objection, however, did not apply to the plain cellophane, which was therefore employed.

It was essential that the substance which sealed the cellophane to the skin should be nonirritating to most skins and should possess strong adhesiveness. Flexible collodion, U.S.P., had served only fairly well for this purpose. I found that some of the propietary collodions held more firmly, yet I hesitated to use them, since their formulas contained substances such as benzol, Canada balsam, castor oil, and essential oids, which might act as excitants of contact dermatitis. The aid of several laboratories was enrolled to provide a collodion free from such objectionable materials. Johnson and Johnson finally succeeded in making an experimental collodion† which has been found to be practically nonirritating to the skin of normal persons and to skins irritated by adhesive plaster.

A number of propietary cellophane adhesives were tried, but these were discarded either for lack of adhesiveness or because of their known resin content. Duo liquid adhesive, a surgical dressing which is an aqueous rubber suspension, was also utilized but was not satisfactory for fastening the cellophane to the skin.

The most convenient receptacle for keeping collodion is a shallow, wide-mouthed glass jar with screw cap tightly stoppered. Thickening of the liquid during exposure, from evaporation of solvents, may be corrected by adding small amounts of acetone. Evaporation will be minimized if the jar of collodion is stoppered whenever there is any long interval between tests.

For applying the adhesive, a test tube without a lip is used, or a short length of glass tubing with smooth ends, of a diameter about

*The following information is obtained from the specifications in patent No. 1,737,187, United States Patent Office, by William Hale Church and Karl Edwin Prindle. A composition is employed which comprises a base (30 to 70 per cent), gum or resin (30 to 60 per cent), a wax or waxlike material (2 to 6 per cent), and a plasticizer (5 to 30 per cent). The base is preferably a nitrocellulose of the pyroxylin type; although cellulose acetate or ethyl or methyl cellulose may be employed. For the gum, gum dammar is very satisfactory, though others may be used, as ester gum, rosin, gum mastic, or the copal resins. A high melting paraffin is favored for the wax, though ceresin wax or beeswax may be used. For plasticizer, tricresyl phosphate, tri-phenylphosphate, di-amyl phthalate, dibutyl phthalate, or castor oil is utilized. In the manufacture of moisture-proof cellophane about 0.00010 inch is applied to each side of the cellophane which usually has a thickness of 0.0007 inch to 0.002 inch.

†The formula of this experimental collodion is the following:

Acetone pyroxylin solution	6 parts
Acetone (highly purified)	2 parts
Amyl acetate (highly purified)	2 parts
Sesame oil	½ part
Ether	2 parts

one-sixteenth of an inch less than that of the cellophane disc. The tube is touched to the surface of the collodion, care being taken not to dip too deeply into the liquid. By placing the tube on the skin and slightly rotating it alternately clockwise and counter-clockwise, a ring of collodion is stamped out. The disc of cellophane is at once fitted over the ring of adhesive and is held by gentle pressure with a gauze sponge. When tests are performed on the forearm, which is the site of selection for this technic, the patient can press down the sponge with his other hand, while the operator proceeds with the next test. After a little practice the procedure can be easily carried out by one individual without any assistance.

Between tests the tube should be stood up in a rack, with the moistened end up. Should the tube end become thickly coated with dried collodion, the latter can be easily removed by wiping with a sponge moistened with acetone.

Although the discs adhere firmly after the collodion has dried, it frequently happens that the mechanical rubbing and pulling of the clothing dislodges them. For this reason the trunk is less suitable for testing purposes than the flexor surface of the forearm or the lateral exposure of the arm. To insure better fixation of the discs, after the collodion is nearly dried, a stockinette type of sleeve is carefully rolled on over the arm, and held in position at each end by a pair of adjustable elastic arm bands.

The discs are removed in twenty-four hours, and the collodion is easily dissolved off the skin by gently rubbing with acetone. A ring of erythema, corresponding to the margin of the disc, is occasionally seen after removing the cellophane. This is caused by the friction of the disc edge against the skin and is transient. Also, at the site of the cellophane disc the skin at times appears slightly pale and occasionally edematous, but these changes rapidly disappear within a few hours and do not interfere with the reading of the test. Rarely a ring of pigmentation is seen after a few days at the site of the collodion. This, too, is nonspecific and of no importance.

The substance to be tested is placed on the skin before the above procedure is carried out. The test material, if solid or semisolid, is applied directly to the skin, or if it is a liquid, is absorbed in a small piece of blotting paper or linen and is applied in that fashion. Care must be exercised, however, not to supersaturate the blotting paper with the fluid.

It has been found that the test material is best applied in the form of a paste or an oil or as a dry substance. Aqueous and alcoholic solutions are not so suitable because of rapid evaporation. Water, moreover, causes wrinkling of the cellophane disc. This disadvantage led

me to experiment with other modifications in the disc membrane liquid adhesive technic. My experience with other substances may be briefly summarized as follows:

(1) Gauze or scrim, laminated on two sides by No. 300 moisture-proof cellophane,* affords a membrane which wrinkles very little and adheres well with the collodion. It must be borne in mind, however, that since the moisture-proof coating contains resin, this membrane should not be used in cases of specific adhesive dermatitis. Scrim, however, produces no irritation in cases of nonspecific adhesive dermatitis.

(2) Batiste cut into discs can be used with the collodion, but does not hold well and may need reinforcement.

(3) Oiled silk fastened with collodion has been found to retain the moisture of the test material. The filling in the silk, however, tends to soften at the edges. It should be borne in mind, moreover, when using oiled silk that it is a proprietary product which is subject to changes in formula, and that linseed, cottonseed, or tung oil may be used in its manufacture. The use of batiste as mentioned is likewise subject to similar criticism, as the nature of the oil varies.

(4) A heavy tracing paper may be used instead of cellophane. The test substance should then be of solid or semisolid consistency.

(5) Duo liquid adhesive, as previously mentioned, was found unsatisfactory when used with cellophane. This adhesive is a water dispersion of rubber latex, and because it evaporates but slowly and is noninflammable would obviously have distinct advantages as a fixing substance. The membranes mentioned in the foregoing paragraphs, however, were poorly fixed by duo adhesive. The latter proved much more effective when used with discs cut from white rubberized cloth faced on one side only. This combination of duo and rubberized cloth has worked so well as to merit consideration for routine use in patch testing in all types of cases. Double-faced rubberized cloth was not found satisfactory.

Duo adhesive is supplied on the market at present in collapsible tubes. For purpose of patch testing it is most convenient to empty the tube into a wide-mouthed shallow jar. It will keep well in such a container if the latter is kept tightly stoppered. In fact, the fixing property of duo seems to improve as it thickens. One need merely add new duo from the tube to the old duo in the flat jar, as it is needed.

In surface testing, the test substance is placed on the skin and a ring of duo is stamped around the material as in the collodion-cellophane technic. The rubber disc is then applied with the cloth side to the skin, and the edges are pressed down with a gauze sponge or small towel. When properly used there is no excess of the duo at the

*Designated as No. 100 and No. 802, made by the Dobeckmum Co., Cleveland, Ohio.

margins of the disc. Two or three rings can be stamped out at a time if one works quickly. Preferably the outer surface of the arm is used, and as many as three dozen or more tests can be applied at one time on the arm of the average sized adult.

After twenty-four hours the discs still firmly adhere to the skin. The outer rubber facing retards evaporation of liquid test substances, so that on removal of the disc the blotting paper or linen used to incorporate the test materials is usually found to be moist. The duo comes away with the rubberized cloth, and, though the skin at times may show an indication of erythema at the site of the ring, this is transient and lasts only a few hours. It is a mechanical effect and is usually of little importance. Occasionally, however, a skin will show a greater degree of erythema followed by pigmentation after a few days, but this phenomenon does not interfere with the reading of the test reaction. An example of this occurred in one subject, with a dermatitis later found to be due to odorono, who showed such irritation to adhesive that the regular patch test could not be used. Since there were no reactions to the ingredients of adhesive plaster, the irritation from adhesive was not considered specific. Duo in this case produced a greater degree of erythema than was previously noted in other subjects, and pigmentation was also evident after a few days. The reaction was strictly limited to the ring of the liquid adhesive, and did not interfere with the reading of the tests. The subject, moreover, showed a greater reaction to duo and to frisket (infra) than did a patient with a severe case of specific adhesive dermatitis. Such skins will not tolerate well any kind of mechanical irritation. It should at this point be borne in mind that, in the case just illustrated, the collodion-cellophane technic produced much less reaction than did the duo rubber disc procedure.

Lotol,* a rubber latex product with colloid, and less viscous than duo, was also tried. It did not fix the discs to the skin as well as did duo.

(6) The objection to the skin irritation from adhesive plaster in patch tests led Shelmire[15] to seek another mode of testing for these subjects. He used various liquid cements and glues, and finally showed preference for frisket because of its great elasticity and inexpensiveness. The rubber cement was kept in ointment tubes. After the test substance was placed on the skin it was "rimmed" with the cement expressed from the tube and covered by a circle measuring one and three-fourths inches cut from Duretta or bird's-eye cloth. Excess cement was rubbed away from the edge of the patch. He claimed that these patches could be kept on for four or five days and the patient

*Lotol, made by Naugatuck Chemical Co., Naugatuck, Conn.

allowed to bathe. In addition, Shelmire stated that in testing large numbers of eczematous patients, he had never observed more than a transient erythema due to the cement.

The formula for frisket is not given in Shelmire's article; however, I have been informed by a member of a concern which manufactures a frisket type of cement that it is made from India rubber and a high test naphtha. In general, rubber cements are made from India rubber and a good solvent, such as chloroform, carbon bisulphide, naphtha, or gasoline, to which are often added rosin, shellac, turpentine, linseed oil, or gum mastic.[15]

Stamping out a ring of frisket by means of the glass tube was tried, and found to be quite feasible, though the rubber cement pulled in strings as it became thicker, because of evaporation of the solvent. The single-faced rubber discs when used with frisket were found to fall off; whereas discs made from a sheet of surgical rubber adhered to the skin quite well. To me the use of such material as bird's-eye cloth did not seem proficient when the test substance was liquid.

I am inclined not to favor this cement because of its inflammability, and because of its rapid thickening, resulting in stringiness when used with the stamping technic. Moreover, the membranes which I had been using for retarding evaporation of the test solvent were not anchored well to the skin by this cement. Furthermore, several instances of definite skin irritation by frisket were encountered. The patient mentioned above, who was sensitive to odorono, showed a 2° (Bloch) reaction to frisket, whereas duo adhesive was better tolerated, only a transient erythema being produced.

SUMMARY

The phenomenon of skin irritation from adhesive plaster has led to a formidable problem, in view of the extensive use of adhesive plaster clinically and as a constituent part of the patch test. I have undertaken a series of studies to determine the nature of these skin changes. In order to begin these investigations it was necessary to develop a technic for testing, by the patch or surface method, those subjects by whom adhesive plaster was not tolerated. In principle, this newly adopted procedure consists in stamping out, by means of a glass tube, a ring of some liquid adhesive or fixing agent around the test substance, and sealing this over by a disc membrane cut from some impermeable or nearly impermeable material.

Several combinations are herein suggested, namely, plain cellophane and collodion (experimental), scrim cellophane and collodion (experimental), tracing paper and collodion (experimental), white single-faced rubberized cloth and duo liquid adhesive, rubber tissue and

frisket type rubber cement. There exists a distinct need for a number of such substitute technics for patch testing, inasmuch as a combination suitable in one subject may be unsuitable in another.

I prefer the technic employing rubberized cloth and duo adhesive for the reasons previously designated, and suggest this as a starting point when the problem of adhesive irritation arises. In fact, it has been found entirely satisfactory to use this procedure routinely in testing for contact dermatitis.

I also desire to point out that cellophane, which is used extensively in the patch test as a constituent part of it, may be of the moisture-proof kind, the surface coating of which contains a natural resin. This variety of cellophane may thus produce misleading positive reactions in selected instances.

The writer is indebted to the members of the Research Laboratories of Johnson and Johnson, who have cooperated to the utmost in technical experiments in connection with this work.

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THE MECHANISM OF MIGRAINE*

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MANY theories have been formulated during the past century concerning the mechanism of migraine. Auzias-Turenne[1] in 1849 stated that migraine was a pain in the head resulting from compression of the trigeminal nerve, particularly its ophthalmic branch, this compression being produced by an accumulation of blood in the sinuses at the base of the brain, principally the cavernous sinus.

Auerbach[2] in 1913 came to the conclusion that the symptom-complex could be best explained by the assumption that the hemicranial disposition is based upon a disproportion between the cavity of the skull and the volume of the brain and that the attacks are evoked by occasional causes, which by way of vasomotor action are disposed to increase this disproportion. Spitzer, quoted by Auerbach, proposed the theory that migraine was due to a temporary stenosis of the foramen of Munro resulting in marked distention of the lateral ventricles followed by edema of the brain.

Vallery-Radot and Blamoutier[3] believed that migraine should be considered an angiospasm and that the sympathetic nervous system may be either stimulated by direct action or mediated by a hemoclastic crisis. Dollken[4] considered migraine a disturbance of the tension and equilibrium of the three vascular categories, consisting in contraction of the arteries, dilatation and increase of permeability of the capillaries, and dilatation of the veins. He thought the etiology was an exudative diathesis produced by an autotoxin, a product of intestinal putrefaction.

Rodella,[5] quoting Hahn, explained migraine as a crisis of the cerebral vessels producing what he termed "angina cerebri." He stated that three phases occur in the production of the attack: (1) a vascular spasm in the region of the large and medium sized arteries and veins, especially of the vertebral vessels; (2) a subsequent vascular dilatation due to liberation of vasodilating substances in the ischemic region of the brain; and (3) the formation of an exudate or transudate in the pia. Rodella examined the eyegrounds of a patient during the stage of dilatation and found widening of the retinal vessels. Critchely[6] noted engorgement and tenderness of the temporal vessels with changes in the conjunctival and retinal vessels and concluded that these findings are suggestive of a vascular origin of migraine.

*Read before the Southern Medical Association, St. Louis, November 21, 1935.

All these theories have some anatomic or clinical fact as their basis, but no one theory so far expressed accounts for all the symptoms occurring in a typical attack. These hypotheses are based on observations without the cranium and not within the skull where the actual mechanism or pathologic physiology of migraine occurs.

I have had under my care for the past five years a young woman who has suffered with typical migrainous attacks for as long as she can remember. Her case is singular in that she has had her brain explored through a burr opening over the left frontal region of the skull. The observations made upon this patient suggest the pathologic physiology of migraine.

CASE REPORT

This young woman, twenty-six years old, a registered nurse, was first seen by me in April, 1931. Her chief complaint was periodic headaches followed by nausea and vomiting, present since childhood.

Present Illness.—The patient knows when a headache is approaching, for she feels languid for twenty-four hours before its onset. The pain begins over the right eye and gradually radiates backward, eventually covering her entire head. At the height of the pain she becomes nauseated, and vomiting ensues. The headache lasts from twenty-four to seventy-two hours. She obtains no relief from ordinary palliative procedures except she thinks that by darkening her room and avoiding all noise she is more comfortable. She found that the ingestion of wheat will consistently produce a typical attack and that this is the principal offending allergen.

Family History.—She has four brothers. One has asthma, and another brother has hay fever. Otherwise, the history is irrelevant.

Past History.—Tonsils were removed when she was a child. Sinus operation was performed in January, 1927, otherwise, the patient has always been well except for headaches. Menses were normal.

Physical Examination.—Except for a depression in the left frontal region of skull about 1 inch in diameter the examination, including neurologic check-up, was negative.

Laboratory Examination.—The blood count, urinalysis, basal metabolic rate, blood Wassermann, blood nonprotein nitrogen level, blood calcium content, and spinal fluid were all within normal limits.

X-Ray Examination.—The teeth were negative. There was some thickening of the mucous membrane of all the sinuses. The chest showed some hyperplastic thickening of the hila and the bronchopulmonary lymphatics. The skull showed an opening in the left frontal region about 1 inch in diameter with smooth borders. Blood vessel markings were increased in frontal regions, otherwise negative.

Allergic Study.—The patient was found sensitive on skin testing to the following allergens:

wheat	lobster	cantaloupe
milk	crab	cocoanut
cheese	oyster	ginger
barley	scallop	grapefruit
corn	shrimp	chicken feathers
celery	almond	duck feathers
lettuce	pecan	goose feathers
parsnip	squash	dust
codfish	cabbage	

Summary of Hospital Record and Operation.—The patient was admitted to the Baptist Hospital on May 12, 1927, on the neurosurgical service of Dr. R. E. Semmes. Her chief complaint then was intermittent headache recurring at increasingly frequent intervals for the preceding six weeks. There was disturbed vision in the right eye.

General medical and neurologic examinations were negative except for a definite choroiditis in the right eye, probably secondary to dental infection. The spinal fluid and other routine laboratory procedures were negative.

X-ray of the skull may 10, 1927, showed blood vessel lines over both sides of skull with very marked concentration over the left frontal. There was some dilatation of blood vessel lines with some skull thinning over the parietal and frontal bones just to the left of the median line. Another similar area was noted over the parietal bone on the left. These changes suggested tumor. Sinuses were negative.

Preoperative diagnosis was (1) tumor of brain, (2) chronic cerebral edema.

Operation.—Craniocerebral exploration was performed through a burr opening under local anesthesia. The patient was having a severe headache at the time. Ventricular puncture and drainage with air injection were performed. An incision was made in the left frontal region at the site of suspicious bone change as shown on x-ray. The dura was tight, nonpulsating, but the blood vessels appeared dilated. The dura was opened and a quantity of fluid escaped under increased pressure. The brain was wet as far as could be observed through the opening made. No tumor could be found. The lateral ventricle was punctured, and fluid escaped under increased pressure. Air was injected into the ventricles for a ventriculogram, which showed no evidence of tumor.

The postoperative diagnosis was edema of brain and idiopathic migraine.

Following the exploratory operation observations of migrainous headaches show the following:

For twenty-four hours preceding the headache the patient is languid; her complexion at first is sallow, but after a time her face appears

blanched and a well-defined pallor is noted before the onset of the pain. There is a definite depression in the region of the opening in her skull. This area has a sunken appearance (Fig. 1). There is a peculiar stare in the eyes, and a hollowness is noted in the orbits. The pain begins over the right eye, gradually spreading over the right side of the head, finally involving the entire head. She avoids light and all noises. The depression in the skull, noted before the onset of the headache, begins to fill up, gradually assuming the appearance of a tumor, which can be easily seen and palpated as shown in Fig. 2. This bulging at the site of operation is not tender and does not pulsate. It does not feel as if brain tissue is protruding through the skull opening; it gives the sense of fluctuation plus a definite tenseness.

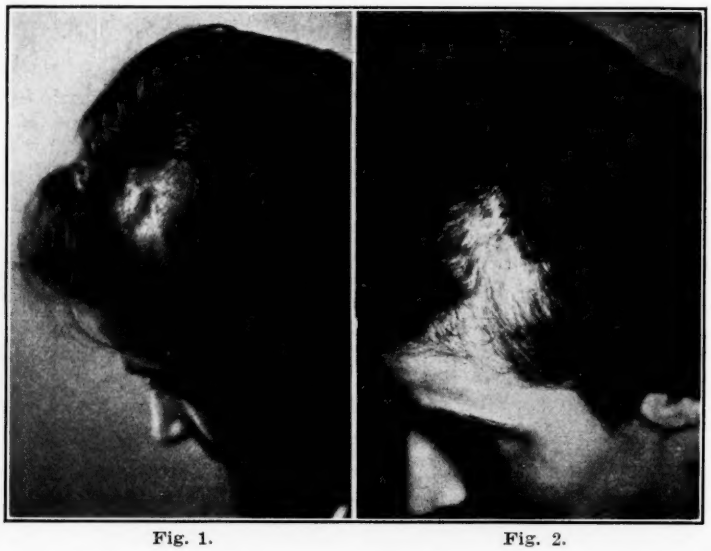

Fig. 1. Fig. 2.

Fig. 1.—Taken in an interval when the patient was free from headache and concomitant symptoms. Note depression in left frontal region at site of operation.

Fig. 2.—Taken at height of pain during a migrainous attack. Note that depression previously seen in Fig. 1 has been obliterated.

As the pain becomes severe, vomiting ensues. The pallor of the face noted before subsides, and the face appears flushed. This process continues from twelve to seventy-two hours and then gradually disappears. At the termination of the attack she goes into a deep sleep, apparently exhausted, and the swelling in the left frontal region gradually recedes until it again assumes the appearance of a definite depression in the skull as shown in Fig. 1.

The following facts in the history and physical findings in this case may be emphasized: (1) the history of her present illness is that of typical migraine; (2) the family history was positive for allergic disease; (3) general medical and neurologic examinations were negative; (4) the patient was found to be definitely allergic and has been relieved

of her symptoms by allergic therapy; (5) craniocerebral exploration was performed while she was suffering from an attack of severe headache.

From the operative findings of Dr. Semmes and the postoperative observations made personally, I feel that the following points are worth consideration:

1. There is at first a vasomotor spasm as evidenced by blanching of the face and persistence of the depression in this patient's skull. Other features of the aura observed by others, such as numbness and tingling, eye symptoms, etc., may be due to vascular spasm with subsequent temporary ischemia of the brain or parts of the brain.

2. There was secondary vascular dilatation with resulting edema of the brain, the severity and extent of which depend on the degree and duration of vasomotor stimulation. This swelling of the brain probably produces a temporary disproportion between the size of the cranial cavity and its contents, a condition in accordance with Auerbach's theory. Vascular dilatation and a wet brain were found on exploration. This evidences itself postoperatively by a bulging in the left frontal region during a migrainous attack in the patient reported.

3. There is a temporary hypersecretion of cerebrospinal fluid, and hyperabsorption of cerebrospinal fluid occurs simultaneously with or immediately following hypersecretion. The cerebrospinal fluid is rapidly produced and is absorbed just as rapidly. According to Weed,[7] the passage of the cerebrospinal fluid into the large venous sinuses of the brain through the arachnoidal villi is purely a matter of filtration from a point of higher pressure to one of lower pressure. If this be so, then with increased pressure within the subarachnoid space there must be a more rapid absorption of fluid. This hyperabsorption tends to equalize the pressure within the subarachnoid space.

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THE LEUCOPENIC INDEX IN ALLERGIC DISEASES*

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IN 1934 Vaughan[1, 2] published two papers dealing with the leucocytic response following the ingestion of foods to which his patients were either allergic or nonallergic. In the first instance he usually found a leucopenia and in the second a leucocytosis. He designed this phenomenon as the leucopenic index. His reports indicate that this test is a valuable adjunct to the previously employed diagnostic measures and that, in some instances, this test alone was of value in determining the etiologic foods.

This communication is an exposition of this test in 537 instances in 56 different patients whose symptoms included hay fever, perennial vasomotor rhinitis, asthma, eczema, urticaria, and migraine.

TECHNIC OF THE TEST

Since many factors modify the leucocytic response, it is necessary either to eliminate them or to reduce them as near as possible to a constant. One must eliminate the factor of exercise and emotional response. The test meal should be prepared with due regard to the amount and the physical state. The temperature at which the food is eaten should be constant. When these precautions are taken, one is able to obtain a very satisfactory series of counts.

The interpretation of the leucopenic index is made upon two bases: first, the maximum increase or decrease as compared to the initial count; and second, the type of curve obtained by plotting the series of counts. This necessitates the development of an intimate knowledge of a series of leucopenic indices in clinically controlled cases using ten-, fifteen-, or twenty-minute counts.

The leucocytic responses reported in this paper were made at twenty-minute intervals, one just before eating, and three after the meal. A few were studied an additional hour at thirty-minute intervals. The information gained by these additional counts did not warrant their continuance. All tests were made upon a fasting stomach or five hours after intake of foods.

THE LEUCOCYTIC RESPONSE

For the purpose of clinical application the leucocytic responses may be grouped under three general types:

First, the negative leucopenic index, a postingestive increase of the leucocytes of at least 1,000 cells as a maximum, and definitely greater

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than the initial count for at least an hour. This would include Curves 1, 2, and 3 of Fig. 1. Clinically these counts are not associated with symptoms.

Second, the indeterminate leucopenic index; a change in the white cell count of less than a thousand during the first hour. This group will include Curves 4 and 5 of Fig. 1. There is little information gained from this type of response.

Third, the positive leucopenic index; a decrease of 1,000 cells or more. This will include Curves 6, 7, and 8 of Fig. 1. Since 90 per cent of

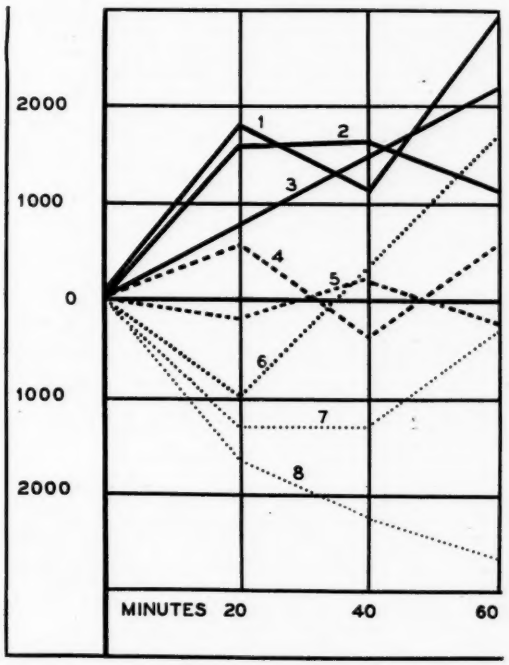

Fig. 1.—Three types of curves obtained by plotting leucocytic response at twenty-minute intervals. The solid line represents the negative leucopenic indices, the interrupted line represents the indeterminate leucopenic indices, and the dotted line represents the positive leucopenic indices.

these indices are associated with clinical manifestations of hypersensitiveness, one may from a practical standpoint consider this type of leucocytic response indicative of allergy.

The first three curves were never associated with symptoms either during the test or within twenty-four hours. After foods giving this type of leucocytic response were taken repeatedly over a period of time, it was found that in 13 out of 59 instances clinical allergy developed, and then these foods gave either an indeterminate or a positive leucopenic index.

It should be emphasized that while the negative leucopenic index, Curves 1, 2, and 3, were not associated with symptoms, this does not

infer that these indices were constant. The rate at which this response may vary is of extreme importance in the practical application of the leucopenic index.

Vaughan[2] mentions the length of time required for the leucopenic index as its chief disadvantage. In an attempt to determine if a single count taken forty minutes after eating was of diagnostic value, a series of 260 leucopenic indices have been analyzed (Table I).

TABLE I

DIAGNOSTIC VALUE OF THE FORTY-MINUTE COUNT

(BASED ON 260 PROVED LEUCOPENIC INDICES)

TYPE OF INDEX	NEGATIVE L. INDEX	INDETERMINATE L. INDEX	POSITIVE L. INDEX
Number of cases	70	78	112
Leucocytic response increased at 40 min.	70	28	0
Leucocytic response decreased at 40 min.	0	50	112
Foods caused symptoms at test or subsequently	13	42	101
Accuracy of 40 min. count compared to clinical observations	81.5%	84%	91%

SPECIFIC OBSERVATIONS

Forty-five leucocytic indices were made with foods known to precipitate symptoms. Of these, every food produced a drop in the white blood count, the least being 200, the greatest being 5,800 with an average of 1,538.

In these same patients 40 foods, known to be without effect allergically, produced an increase of the white blood count in every instance, the increase being from 200 to 8,000 with an average of 1,685.

In five asthmatic patients 48 counts were made after ingestion of foods which were known to precipitate asthma. In case one, there were seven foods causing an average leucopenia of 1,606; in case two, six foods depressing the count averaged 1,250 cells; in case three, nine foods accounted for an average loss of 1,600 cells. Case four averaged a loss of 2,570 cells for 10 foods; while case five averaged a leucopenia of 1,700 with 16 different foods.

A patient with migraine lost an average of 1,800 cells in 17 different tests and responded clinically with elimination of these foods. A patient with perennial vasomotor rhinitis lost an average of 1,300 cells with 12 different foods.

Gay,[4] in a series of 12 gastrointestinal patients found that 55 foods which were not a cause of symptoms produced an average increase of 1,235 cells; whereas in these same patients 75 foods known to be a cause of symptoms produced an average decrease in the white blood cells of 1,381.

In 139 instances in which foods definitely increased seasonal hay fever symptoms, a loss of white cells occurred in every instance. The depression of the leucocytes was from 200 to 3,200.

The clinical symptoms are not always in direct ratio with the depression of the white blood count. For instance, a patient with an indeterminate reaction to milk required 23 injections of adrenalin to control his

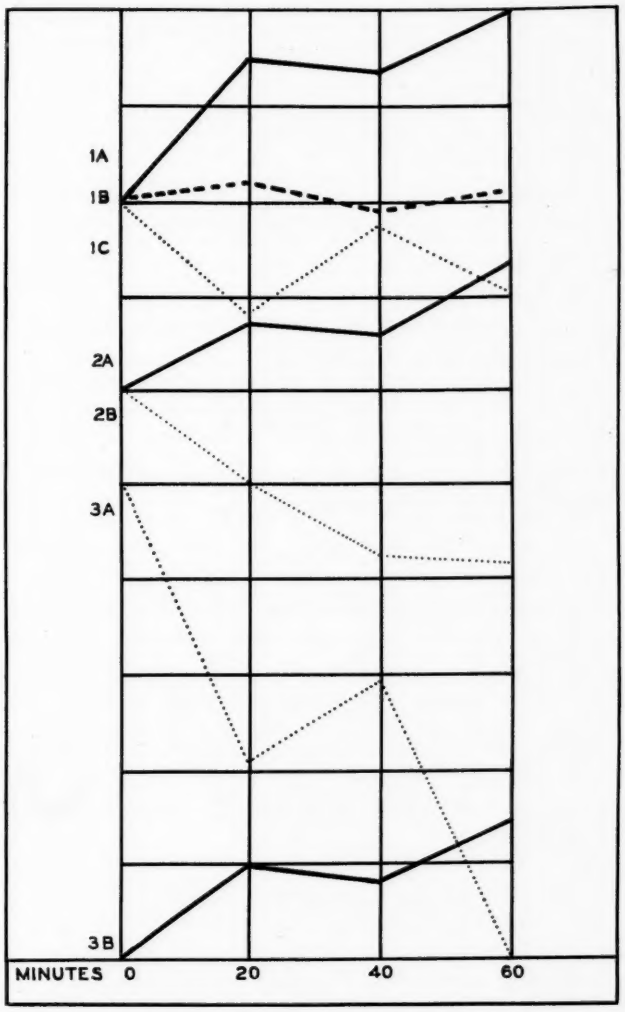

Fig. 2.—The modification of the leucopenic indices with continuous use of a food. The ordinates represent 1,000 cells, the abscissae, twenty minutes.

Curve 1*A*, carrot test made Feb. 23, 1935; 1*B*, same food test made March 5, 1935; and 1*C*, carrot test made April 11, 1935.

Curve 2*A*, rice test when first used in diet; 2*B*, after being used three weeks.

Curve 3*A*, pork test made Nov. 27, 1934; 3*B*, pork test made Feb. 23, 1935, after avoidance of pork during the intervening period.

symptoms. On testing with fish he developed a leucopenic drop of 3,100 cells in twenty minutes but needed only three injections of adrenalin to control his reaction.

A feature of the leucocytic response of considerable clinical importance is the variation of the leucopenic index after a food has been eaten constantly as compared to the response when used rarely.

These successive changes are illustrated in Fig. 2. In the first instance a patient with asthma was found to tolerate carrots and gave a negative leucopenic index. Twelve days later another count was of the indeterminate type, while a third count made a month later was definitely positive and was associated with symptoms. In a second patient with migraine, sensitive to wheat, a rice test gave a negative leucopenic index. Substitution of rice for wheat brought about relief for three weeks and then symptoms gradually recurred. It was found that the rice gave a positive leucopenic index, and upon its elimination there has been subsequent and long continued improvement. In another patient the ingestion of pork for a leucocytic test in November, 1934, was followed by severe symptoms and a loss of 5,800 cells in one hour's time. Avoidance of pork until February, 1935, brought about a degree of tolerance as evidenced by a negative leucopenic index and an absence of symptoms.

In a fourth patient it was found that a leucocytosis of 3,100 cells following pineapple changed to a leucopenia of 1,100 cells after using the food four times in forty-eight hours.

THE FORTY-MINUTE DROP

A secondary drop has been observed in 30 counts, 19 of which were later associated with clinical allergy. Counts with secondary drops are frequently seen with foods which with constant use cause definite symptoms.

The reverse action has been observed. When a food gives a strong depression of the white count and is omitted for a period of time, the response is more favorable, and, when negative, the foods are temporarily not a cause of allergy.

LIMITATIONS OF THE TEST

Since the leucopenic index is usually not stabilized except in the case of foods which have been used constantly, one should limit one's selection of tests in the earlier stages of diagnosis to those products which ought to have a fixed reaction. Later on the tests will be of value in measuring the degree of tolerance and may guide one in governing the diet.

The test is most valuable in that one can select with it those foods which are not a cause of symptoms at the time of the test.

The efficacy of the test for general purposes will depend upon the accuracy of the count, the previous ingestion of the food, and an unknown

factor, which may be designated as *the ability to maintain tolerance.* This factor is quite variable, being practically constant in some cases and in others almost nonexistent.

THE CLINICAL APPLICATION OF THE LEUCOPENIC INDEX

Since many factors may account for a variation in the leucocyte counts, the first prerequisite for the clinical use of the leucopenic index is that of accuracy in making the leucocyte counts.

The leucopenic index as a diagnostic measure in food allergy must be used with due consideration of the modifications of the leucocytic response as indicated in this communication.

In our experience the leucopenic index has proved of value in patients with intractable asthma with negative skin reactions in whom symptoms were of such nature that clinical tests could not be made. It has also been found that some patients do not exhibit a negative leucopenic index to a single food, or if they do have this response they are not able to maintain it with prolonged use of the food. The exact nature of these cases is yet to be determined. Zeller[5] has reported this same observation in a series of intractable asthmatic patients. In one case of asthma only potato and tomato produced a negative leucopenic index, and all other foods used in the diet produced positive leucopenic indices, the average loss of white cells being 2,570. On clinical trial the patient ate potato and tomato for two weeks with absolute freedom of symptoms. Asthma promptly recurred upon feeding foods which had produced positive leucopenic indices. This study definitely indicates the diagnostic value of the leucocytic response.

SUMMARY AND CONCLUSIONS

It has been shown that a postmeal leucocytosis was usually associated with foods not producing allergy; whereas leucopenia or an indeterminate count was associated with those producing symptoms.

The accuracy of a single forty-minute count is about 80 per cent that of the three postmeal counts.

Several cases of intractable asthma were cleared up promptly using the leucopenic index as an adjunct to other tests. The count was of especial value in these patients because clinical observations were misleading.

It was found that some patients gave either no negative leucopenic indices or so few that no trial diet could be employed. In one patient only two foods agreed according to the leucopenic indices, and this was corroborated by having the patient live on these foods for two weeks and remain absolutely free of symptoms during this time.

In one case of extreme asthma it was found possible to relieve cough and wheezing commonly thought to be due to emphysema.

The leucopenic index is not constant. Its variation from a positive to a negative one has been corroborated clinically.

A significant finding is the fact that asthmatic patients whose symptoms could not be controlled either showed a positive leucopenic index to all foods or were unable to maintain a negative leucopenic index to a food regularly used in the diet.

It is our conclusion from the evidence reported herewith that the leucopenic response has a permanent place in the diagnosis of allergy.

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DISCUSSION

DR. VAUGHAN.—I should like to show a few lantern slides. This year we have run a series of 26 foods that were known to cause trouble, and we ran them for a total period of four hours, with half-hourly counts.

(Slide) The two positive reactions to chocolate were in persons known to be sensitive to chocolate. When they ate it, they had acute symptoms. The negative curves were from negative controls.

(Slide) As to when the test should be done, apparently it is best done somewhere between thirty and sixty minutes after eating. Our present technic is three counts, at one-half hour, one hour, and one and one-half hours. That gives us more information. When one count is done, we get 85 per cent of the reliability obtained when three counts are made. This curve is for the woman I spoke of earlier (see discussion of "Observations on Acne, etc." by T. D. Cunningham) who was sensitive to beef. At the end of the hour, she became violently nauseated and vomited six times. The physical mechanism of vomiting may account for the change from a leucopenia to a leucocytosis. I think serial counts are probably better. In this beef case, for example, a single count after sixty minutes would have been positive. But a single count after ninety minutes would have appeared to be negative.

(Slide) I wanted to run a negative control on onions. One of the girls in the laboratory volunteered. She loved onions. I ran the control and it turned out positive. That was too bad. The next day she was sick in bed with an attack of migraine. When she got back to the office, we skin tested her with onion and she was positive.

In this series of responses to known offenders, the leucopenic index corresponds with the known sensitizations in 81 per cent of the cases. The skin test corresponds in only 64 per cent. Theoretically a combination of both testing methods would be still more accurate.

I wish to thank Dr. Rinkel for his interest in the leucopenic index and hope that others will find it of aid, at least in doubtful cases.

DR. RALPH H. SPANGLER.—Does the leucopenia tend to be of a polymorphonuclear or a lymphocytic variety? While my experience has been limited in attempting to interpret the index, the type of cell in the differential count has interested me.

One patient came to my office last week with a marked urticaria of undetermined origin. Her total white count was 7,400; the differential count showed 58 per cent lymphocytes, 41 per cent polymorphonuclears, and only 1 per cent eosinophiles. Ten minims of a 1:1,000 solution of adrenalin were given hypodermically, and in about eight minutes the patient was practically free of clinical symptoms. Within another ten minutes a second white count was 10,600, and the range of the differential count changed to lymphocytes 26 per cent and polymorphonuclears 74 per cent. No eosinophiles were found in counting 200 cells.

In several instances of food hypersensitivity I have had similar experiences. When the patient is relieved of symptoms, the predominating type of cell in the differential count changes from a lymphocytic type during the stage of leucopenia to a polymorphonuclear type when the total number of leucocytes have again risen.

DR. RATNER.—What happens to the eosinophile count during the drop?

DR. RINKEL.—I should like to say we have made no study concerning whether the increase in white blood cells was primarily of the lymphocytes or the polymorphonuclear cells. Neither have we carried out a study of the changes in the number of eosinophiles following the ingestion of a food. I did that some time ago and did not find it of sufficient value to continue it. The value of the leucopenic index is so much greater than the study of the eosinophilic response that we have not studied the latter at this time.

BRONCHIAL ASTHMA*

Results of Treatment in 207 Patients Under Observation for a Period Varying From One to Thirteen Years

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IN AN EFFORT to obtain as correct information as possible regarding the end-results in my patients who are or have been suffering from bronchial asthma, the following procedures were adopted. I wish to thank Dr. F. M. Rackemann for his suggestions.

A questionnaire with a self-addressed, stamped envelope was mailed to all of those who were no longer under treatment. This brought in a fair number of replies and repeated questionnaires brought in a few more. Personal telephone calls were sometimes necessary. The referring physicians reported the condition of several.

As soon as the end-result was known, a card containing the important data in history and examination was made out for each patient, and this procedure made the tabulating fairly simple.

No patient was included unless a period of at least one year had elapsed since treatment was started. It would, of course, have been better if the period were longer than one year, even up to five or ten years, but the longer the time the more difficult it is to obtain true information regarding the condition of the patients.

In this study only the records of private patients were used. This markedly reduced the total number available; the clinic at Northwestern University Medical School has had many hundreds of asthmatic patients in the eleven years of its existence. I believe, however, that this survey of the smaller number of private patients has yielded more valuable information than could be obtained from the large number of dispensary cases. The asthmatic patients who come to an office are more intelligent, as a rule, and most of them have cooperated very nicely. In clinic cases the follow-up is difficult unless one has assistants who can go to the homes for personal checking.

DIAGNOSIS AND TREATMENT

By a careful history and physical examination, followed by skin and other tests, all the patients were definitely diagnosed as suffering from bronchial asthma.

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*From the Cook County Hospital and Northwestern University.

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The treatment, whenever possible, was the conventional one based on elimination of the cause of the attacks, with emphasis on strictness in such elimination. Hyposensitization was carried out where complete elimination was impossible, as in those persons hypersensitive to pollen, house dust, orris root, horse dander, and cottonseed. Nonspecific measures, e.g., vaccines, were also used in many cases, and much attention was given to oral hygiene and to removal of foci of infection.

RESULTS OF TREATMENT

The results in the 207 patients studied are tabulated as follows:

Table I shows the number of cases in the decades of onset of symptoms, and it may readily be seen that a large percentage begin their trouble early in life—which conforms to similar published data. The incidence lessens with increasing age, thus differing sharply from the curve in that group of paroxysmal dyspnea due to "cardiac asthma."[1] The cases are then divided into the extrinsic and the intrinsic groups. The former are considered to be hypersensitive to foreign proteins, usually to more than one. All those who do not fit in this group are placed in the intrinsic group, wherein it is thought that their asthma comes from something within the body, as bacteria. It is an ill-assorted group and not well understood. As one can see, the extrinsic cases far outnumber the intrinsic in the early decades. The two groups are approximately equal in the fourth decade; after this the intrinsic asthmatic individuals predominate. It is interesting to note that there were 101 males and 106 females in the series; sex, therefore, is of no importance.

TABLE I

CLASSIFICATION OF 207 CASES OF BRONCHIAL ASTHMA

AGE AT ONSET	EXTRINSIC		INTRINSIC		TOTAL
	MALE	FEMALE	MALE	FEMALE	
0- 9	38	29	1	0	68
10-19	14	11	0	1	26
20-29	12	13	4	12	41
30-39	5	8	3	8	24
40-49	11	3	7	12	33
50-59	1	1	3	6	11
60-69	1		1	2	4
Total	82	65	19	41	207

In Table II the results of treatment of the 147 extrinsic cases are given, and in Table III the intrinsic group is itemized. It will be seen from this that the best results, by far, are obtained in the extrinsic group and in those whose asthma began in the first decade. Cases are called "cured" when they have been entirely symptom-free for at least one year. Those marked "improved" vary in their improve-

ment from approximately 25 per cent to 95 per cent. Only a small percentage of patients were not improved in the extrinsic class; a larger percentage of the intrinsic group was not benefited.

TABLE II

EXTRINSIC ASTHMA—RESULTS OF TREATMENT OF 147 PATIENTS

AGE AT ONSET	"CURED"		IMPROVED		UNIMPROVED		DEAD	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
0- 9	14	6	16	20	6	2	2	1
10-19	3	3	8	6	3	3		
20-29	3	6	8	4	1			2
30-39	2	1	3	6		1		
40-49	1	1	4	1	3		3	1
50-59	1			1				
60-69	1							
Total	25	17	39	38	13	6	5	4

TABLE III

INTRINSIC ASTHMA—RESULTS OF TREATMENT OF 60 PATIENTS

AGE AT ONSET	"CURED"		IMPROVED		UNIMPROVED		DEAD	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
0- 9					1			
10-19								1
20-29		2	2	6	2	4		
30-39	1			5	1	2	1	1
40-49			2	8	2	2	3	2
50-59				3	2	2	1	1
60-69				1			1	1
Total	1	2	4	23	8	10	6	6

In Table IV the results of treatment are summarized. In addition the average blood eosinophilia and the percentage of positive family history are given. The fact that the percentages of these two are almost as high in the intrinsic group as in the extrinsic makes one speculate concerning the possibility that the separation into the two groups may be merely artificial. It may well be that most, if not all, of the intrinsic group really are sensitive to some foreign proteins just like those in the extrinsic class, and we merely fail to find these allergens. It is a fact that house dust extract frequently gives positive reactions on intradermal testing in many such patients. Some may be clinically sensitive to house dust as well, although this is hard to prove. Are they sensitive to bacteria within their body? The

TABLE IV

SUMMARY OF 207 CASES OF BRONCHIAL ASTHMA WITH RESULTS OF TREATMENT

	"CURED"	IM-PROVED	UNIM-PROVED	DEAD	TOTAL	AVERAGE BLOOD EOSIN.	POSITIVE FAMILY HISTORY
Extrinsic	42	77	19	9	147	5.7%	69.4%
Intrinsic	3	27	18	12	60	5.1%	52.6%
Total	45	104	37	21	207	5.5%	64.4%

answer is probably "no" because surgical removal of foci of infection rarely gives more than temporary benefit. Cutaneous tests to bacterial proteins are almost uniformly negative, although intracutaneous tests to killed bacteria and filtrates frequently are positive.

In the 21 patients known to have died, only six passed away during an attack of asthma or from the immediate result of an attack. In three of these morphine was administered and may have been a factor in death. Two were accidentally killed. In six patients death was due chiefly to cardiac decompensation or to cerebral hemorrhage. In five others a complicating condition led to death (infective sinusitis after puncture, pneumonia, empyema, carcinoma of the lung, and gastroenterostomy for pyloric obstruction). In the remaining two the cause of death could not be found.

In Table V there is listed the causes of attacks as far as can be judged both from the clinical facts and from skin tests. It will be noted that dust came first in this series, closely followed by pollen and animal derivatives. Foods were important in 34 cases. In many more persons there were positive tests for foods, but these were not considered causative factors and were, therefore, not listed. Thus, in the ragweed asthmatic persons it was common to find positive tests for vegetables and fruits, but these were omitted because the asthma was undoubtedly due to ragweed pollen, even though these foods may have been, and probably were, factors. There were seven cottonseed cases and only six due to orris root, demonstrating again that while orris root is a common cause of vasomotor rhinitis it is not a common cause of asthma.

TABLE V

IMPORTANT EXTRINSIC FACTORS

Dust	94
Pollen	88
Animals	61
Foods	34
Cottonseed	7
Orris Root	6
Silk	2

It might be interesting to note here that most of the pollen asthmatic persons also had hay fever and that vasomotor rhinitis was present in 42 of the extrinsic group of asthmatic individuals and in 7 of the intrinsic group.

COMMENT

When one looks through the literature on the results of the treatment of bronchial asthma, one is struck by the paucity of reports. Most of us are apparently too busy to undertake the task. It is not easy to follow patients through a period of years and to obtain accurate statistics on their respective conditions.

In the early work of Walker[2] and of Larson and Bell[3] no tables of results are given. Rowe[4] discussed 110 cases in children and young adults and obtained 91 per cent good results, but some of his patients were under observation for only four months. Menagh[5] summarized 300 cases and 85 were considered well, 83 improved and 38 not improved. He felt that surgery of the nose and throat cleared up 31 per cent of his cases and that vaccines aided another 44 per cent. He strongly advocated these two procedures in addition to elimination and desensitization.

All of us are especially indebted to Rackemann for his papers. In 1927 he surveyed 1,074 private and clinic cases with asthma that were followed for at least two years.[6] It is interesting and a bit surprising that his percentages of results are almost identical with those given in our tables. Thus, in each series, approximately 20 per cent are in the "cured" class; about another 50 per cent are more or less improved; about 20 per cent are unimproved; the other 10 per cent are dead. In both series the percentage of "cured" and improved is high in those whose asthma began in the first decade and then steadily decreases with each decade. In both, the best results were obtained in the extrinsic group because the exciting factors are usually not difficult to remove.

In 1928 Rackemann[7] analyzed the 213 patients who had been relieved of symptoms for more than two years. In 1932 he[8] reviewed these same 213 patients, after a lapse of four more years, making a total of six or more. Forty-nine are known to have relapsed; seven of these were in the pollen cases. This demonstrates again how difficult it is to keep pollen sensitive individuals entirely free from symptoms.

From this last follow-up by Rackemann it should be apparent to all of us that bronchial asthma occurs in hypersensitive individuals; that, although one removes the cause of attacks and clinically "cures" his patients, the underlying constitutional predisposition to allergy remains. This is a matter of chromosomes, as noted by Kahn,[9] who concludes that cures in bronchial asthma are not possible. This statement is probably correct in a technical sense, i.e., the constitutional tendency to asthma will probably last through life. Clinically, however, many patients have had complete relief of symptoms for so many years as to amount to a "clinical cure." If by analogy with other diseases we say that a patient free from recurrences for five years is cured, then many patients who had bronchial asthma are and have been completely cured.

One lesson in treatment should be apparent to all of us. Since allergic individuals tend to relapse, we should keep them under observation as long as we can. This does not mean under treatment, necessarily, but we should not discharge them. They should report

back for observation at stated intervals of from one to four times a year, and careful questioning may bring out the point that the patient has become careless with his diet or environment. If so, he should be reminded of the fact that relapses are of common occurrence, and he should be set straight once more. I believe that such management goes far toward maintaining our "clinical cures."

SUMMARY AND CONCLUSIONS

A survey of 207 private patients suffering from bronchial asthma is offered. The patients have been under observation for a period varying from one to thirteen years. The majority belong in the extrinsic group, and the results of treatment in this class are much better than in the intrinsic group.

Bronchial asthma is prone to begin in the first decade of life, and the prognosis in these patients is very good. The older the individual is when symptoms begin, the less favorable is the prognosis.

The high percentage of blood eosinophilia and positive family history in the intrinsic group suggest the possibility that all or at least most asthmatic persons suffer from one or more foreign proteins and not from bacterial infection or other relevant internal conditions.

Approximately 20 per cent of the patients have been clinically "cured" for at least one year; another 50 per cent are more or less improved; about 20 per cent are not improved; and about 10 per cent are dead; only six patients died as a result of asthma. The tendency to relapse should force us to keep our patients under observation for life.

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DISCUSSION

DR. RACKEMANN.—Dr. Unger asked me to open the discussion of this paper. He was good enough to let me see a copy of his manuscript. Such a piece of work as this is a colossal job. I can speak from painful experience, and I can say that it is worth while and that the author learns a lot. "The proof of the pudding is in the eating."

Dr. Unger has told you about his treatment in detail. He might have assumed that we knew his treatment to be all right, and he might have taken a little more time to tell us about the subgroups under the main headings of extrinsic and intrinsic asthma: how many patients had their tonsils out, how many were treated with desensitization, and so on.

In the evaluation of the results of treatment in any group, the various factors are always difficult to control. Perhaps the treatment worked well, and the patient recovered as a result of it; but perhaps there were other factors operative at the same time. Possibly the cat or the dog died at the opportune moment. For example, there was a patient to whom I gave vaccines with great success. She wrote me a very enthusiastic letter, saying how much she appreciated what had been done for her. Then, unfortunately, down at the bottom of the paper, she said, "P.S. Please note my change of address."

Dr. T. D. Cunningham.—I think in reporting asthma cures, we make a mistake ever to say we have an asthma cure, for the reason that we do not know what the underlying principle is in allergy. Therefore, an asthmatic individual, as well as other types of allergic persons, can and does become sensitive to other things during the process of treatment. For example, you test an individual today and he does beautifully with the withdrawal of certain foods, and for several months or several years his asthma will not recur. When you retest him, you will find the variation in the test will vary as high as 25 foods to which he has become sensitive while he may have lost sensitization to other foods. So that it becomes very important, in treating asthma over any period of time, to recheck at frequent intervals, as many as he has recurring attacks of asthma, that is, if the patient is well for any prolonged period. Until we know what the underlying condition is in any individual that makes him allergic, I do not think it is fair to talk about cures. We can talk about relief. I have some patients who have gone ten years with relief and they think they are cured. I am not deceiving myself. I think at any time, under the proper conditions, they may become asthmatic again, following a slight cold or any other disturbance. I think we should keep in mind that we have temporary relief but not cures in the treatment of asthma.

Dr. C. Ulysses Moore.—I want to ask Dr. Unger whether he has tried giving large doses of vitamin D as reported by Reid and Rappaport? If so, with what results?

One hesitates to mention vitamin D in this connection, but it may help to explain the satisfactory results obtained in asthma of children during the past ten years. Our results have seemed too good to report. We have given large doses of vitamin D in some form to every child as an antirachitic measure, not dreaming that this vitamin would help cure the allergic dyscrasia.

My attention was first called to vitamin D in this connection in a letter from Shanghai that came in response to a paper of mine. "The worst case of asthma in Shanghai" was claimed to have been cured by the taking of cod liver oil, prescribed by an English doctor there. Since then so many more corroborating reports have come in that

one can hardly help being convinced that vitamin D is of benefit in cases of allergy. I would appreciate knowing the experience of others who have used it.

DR. GRAFTON TYLER BROWN.—As Dr. Rackemann says, I think it does us all good for somebody to take stock once in a while. I object, however, to one deduction drawn by Dr. Unger. Because the eosinophile average of his intrinsic group was the same as the eosinophile average of his extrinsic group, he inferred that the asthma in the so-called intrinsic group was also due to extrinsic substances which he had merely failed to detect. I should like to stress again the importance of bacterial hypersensitiveness, and call attention to the fact that an increase in the percentage of eosinophiles can be produced by sensitization to bacteria, the same as by sensitization to any other form of foreign protein.

Dr. Unger's eosinophile average for his series of asthma patients is relatively low. In normal nonallergic individuals, the eosinophile average varies from 1 to 4 per cent; whereas Dr. Unger's eosinophile average for asthmatic persons ran only a fraction over 5 per cent. Some years ago, I wrote a paper on eosinophilia in asthma and allied conditions. My eosinophile average for all the asthma patients was about 7 per cent, and was almost exactly the same for the intrinsic as for the extrinsic group. In other words, non-sensitive or bacterial asthma presents just as definite an eosinophilia as does asthma due to sensitization to food, animal epithelium, pollen, or miscellaneous inhalants. Dr. Cooke has reported similar findings and also pointed out that the family history of allergy was just as strong in bacterial asthma as in true atopic asthma.

DR. UNGER.—The reason I did not put the intrinsic cases into subgroups was because I was quite puzzled as to just how he put them into these various subgroups. I decided to group them into what could be definitely proved as extrinsic, and all the rest I called intrinsic.

It was not alone the eosinophilia which led me to believe there may be no intrinsic group. We had a positive family history in 52 per cent of the intrinsic and 69 per cent of the extrinsic. These are both very high, much higher than you would find in normal persons, or than you would get in bacterial cases.

With regard to vitamin D, we all use it in a general hygienic way. We must not become too allergic-minded and forget about the general health of our patients.

As Dr. Cunningham brought out so well, one should recheck his patients, especially children. I make a point of retesting children every two years, if I possibly can, and more often if symptoms recur.

DR. WALDBOTT.—We are all extremely interested in the essential points of Dr. Unger's paper, namely, the fate of patients whom we have followed up for a long period of time. I wonder, however, whether it would not be useful in discussions of this kind to omit such elementary facts concerning the management of the asthmatic individual as formed a large part of his paper with which every one of us is familiar.

Special Reports

SEVERE ALLERGIC REACTION FOLLOWING WASP STINGS WITH SUBSEQUENT RELIEF OF CHRONIC ARTHRITIS

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THE dramatic possibilities of sudden severe reactions following insect stings are well known to the farmer, but in going over the medical literature of the past twenty-five years only a handful of references appear.

The most detailed English report is that by Benson and Semenov,[1] who point out that three factors are involved in allergic reactions to bee stings: sensitivity to the venom itself, sensitivity to allergens intrinsic in the insect body, probably protein in nature, and sensitivity to pollens which may be adherent to the bee. An individual sensitive to any one or all of these factors may react allergically. The authors report a case of a beekeeper in no way sensitive to stings at the beginning of his work eighteen years before, although often stung as many as 75 times in a day. For three years prior to consulting the authors he had developed hay fever symptoms in April, May or June, lasting until October, and made worse after stings. When seen by the authors he had begun to have asthmatic attacks following stings. He was tested by various pollens often adherent to bees, and found mildly sensitive to several. By painstaking work the authors made extracts of the bee bodies and stingers, and also of the venom. The patient was found to be extremely sensitive to these extracts, particularly the protein fractions of body and stinging apparatus. He was treated by increasing doses of the extracts, and was successfully desensitized so that he became able to continue beekeeping without symptoms.

Braun[2] reports the case of a man receiving seven bee stings, each with a more severe reaction, until one minute following the seventh sting, the patient's face became suffused, he complained of a choking sensation, and coughed, then felt bearing down pains, became extremely anxious, and lapsed into coma which lasted for four days. This patient was desensitized by an extract made from bees' bodies, and suffered only mild symptoms thereafter.

It seems possible to induce sensitivity over a period of time in previously non-sensitive persons by frequent exposure to insect stings. Waterhouse[3] and Braun[2] report the development of sensitivity to bee stings, and Hubert[4] to wasp stings. Entomologists, however, cite the

From the Clifton Springs Sanitarium and Clinic.

instance of a farm boy who carried a small cage of bees strapped to his arm, and allowed himself to be stung at intervals, gradually desensitizing himself so that he no longer had any violent local reaction. It is well proved in all work with allergens that the violence of any reaction is a factor not only of the inherent sensitivity of the patient, but also of the dosage of allergens and the frequency of application. These reports illustrate this, and also the fact that insect stings in sufficient number or close enough proximity in time, in a sufficiently sensitive individual, can cause extreme reactions involving shock, coma, and even death. I wish to report a case in which the reaction was violent, but because of its severity appeared to have a beneficial effect on a concurrent disease—chronic arthritis.

On September 4, 1934, I was called to see a seventy-year-old physician's widow whom I had previously treated symptomatically for chronic arthritis involving the back, knees, ankles, wrists and hands. The patient had been cutting flowers in her garden when she stepped in a yellow jacket's nest, and was simultaneously stung in seven places—her ankles, wrists and hands. She hurried into the house to apply soda to these areas which became almost instantly swollen and painful. Within three minutes her "heart began to pound queerly, there were black specks before her eyes," and she felt as if she would choke. I reached the house within ten or fifteen minutes of the injury.

The patient was an active, well-preserved woman, with marked dorsal kyphosis, and hands, ankles, and knees considerably deformed by chronic hypertrophic arthritis. Her face was ashy pale, her lips were pale, respirations rapid, and pulse thready. Her right wrist, both ankles, and left forefinger were red, considerably swollen, with small white urticarial wheals and seven visible fresh sting marks. She had undressed immediately because she remembered as a child seeing an older brother brought home after bee stings. His face and body were so swollen that he was hardly recognizable, and his clothing had to be cut off because of generalized edema. Before she had finished her story, she began to scratch her right wrist, then her abdomen. Her face became suffused, her lips and eyelids began to swell, and over the abdomen and chest came a sprinkling of urticarial wheals which quickly became confluent so that in the length of time it required to get a hypodermic of adrenalin ready, her torso was a solid urticarial welt, yellowish in color, because the usual red surrounding the wheals was obliterated by the severity of the reaction. She had nausea, almost involuntary defecation and urination, and complained of "itching and prickling inside her stomach." Her tongue and throat were swollen, but she had no alarming epiglottal edema or real asthmatic wheezing. She was, however, an extreme and horrible picture of a severe allergic reaction. By the aid of adrenalin and ephedrine, the worst of the reaction was over in an hour, though the patient was prostrated, and patches of urticaria

came and went for three days, particularly at night when the body was warm. Her exact temperature is not known, but was definitely elevated for some hours.

About six weeks later she reported that her arthritis had improved greatly since the wasp stings. She had not been so agile in years and was practically free from pain. This freedom from pain and stiffness persisted for a period of about four months, then gradually the crippling returned.

At the present time, a year later, she is considerably handicapped by the arthritis, getting up and down out of chairs with difficulty. She avoided insect stings during the summer, and has refused any experimental investigation as to whether or not she is still sensitive, and to which of the possible allergens.

Since heat and protein shock are probably still the best treatments available for chronic arthritis, the wasp stings and the ensuing severe allergic reaction seem to have been beneficial therapeutic agents in the course of this woman's chronic arthritis. While speculating on the possibilities of this, the work of Draper[5] who "in desperation" used the "old and homely method of stings of honeybees" to treat chronic arthritis was called to my attention. It has been a lay belief for generations that bee stings help arthritis. Draper noted that "clinically all the cases have shown a very definite improvement in their sense of well-being and in their appearance." He was particularly interested in the sting reaction syndrome. To quote, "Just what the mode of action of the bee sting is, at present, is comparatively obscure, but the effect upon blood count, the skin reaction and the reports of generalized edema and the temperature rise suggest acute protein shock analogous to the effects obtained by the injection of many foreign proteins."

Within the past year, a fascinating book, *Bee Venom Therapy,* has been published by Beck,[6] who cites countless instances of severe reactions to bee stings, including acute anaphylactic syndrome, paralysis, hemaplegia from cerebral hemorrhage, coma, and even death to both man and animals. He outlines the chemistry of the bee sting as analyzed by Flury[7] and Langer.[8] It contains volatile oils which chiefly cause the pain of the sting, tryptophan, choline, glycerin, phosphoric, palmitic and fatty acids, a non-nitrogenous substance probably like cantharidin, and a water soluble acid with strong hemolytic effect, probably a saponin. Contrary to popular belief it contains no formic acid. Physiologically the venom has three factors: first, a neurotoxin capable of causing extensive paralysis and even a respiratory death; second, a hemorrhagin with cytolytic effect on endothelial cells causing increased permeability of blood vessels hence exudation of blood elements and improved oxidation of the tissues—a histamine-like effect; and, third, a hemolytic factor resulting in definite methemoglobin production. In animals killed by bee venom, autopsies show hyperemia of the liver, pancreas, kidneys, even gross hemorrhage into the meninges and pericardium.

Beck, himself, besides quoting extensive European literature showing remarkable results achieved in the treatment of arthritis either by multiple bee stings or the use of sterile injectable bee venom, gives detailed directions for its therapeutic use. He finds that most arthritis, except that of tuberculous, luetic, or gonorrheal origin, is benefited by bee venom therapy. He notes that, in general, beekeepers are free from arthritis and that the arthritic person reacts less violently to bee stings than the normal individual. His patients are given increasing doses of bee venom until they react normally (i.e., vigorously); then they are given further doses to hold the state of reactivity. The treatment takes longer and is less effective the greater the duration of the disease. Beck explains the beneficial results as due to the specific inflammatory effect of the bee venom, itself (the hemorrhagin), which improves the oxidation of tissues. He, of course, avoids any generalized severe allergic reaction.

My patient is of interest because she presented a real medical emergency. Stings about the face and neck, or into a vein, have resulted in death in less than ten minutes. The use of a tourniquet to prevent the rapid systemic absorption of the toxic material might be helpful. Beck reports that alcohol neutralizes bee venom. The chemistry of the wasp sting is unknown. The effect of bee, snake, and black widow spider venom[9] has received considerable attention lately. Cobra venom as an analgesic and a retarder of tumor growths is reported useful in inoperable cancer by Monaelesser.[10] Calmette[11] and many others report the treatment of epilepsy with snake venoms, some of which are antispasmodics. Leprosy and psoriasis also have been treated by venoms. The whole subject of the therapeutic possibilities inherent in naturally produced chemical substances like venoms offers much material for speculation.

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CONTACT DERMATITIS DUE TO GOAT HAIR*

Report of a Case

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GOAT hair hypersensitivity has never received much attention, although this substance is used very extensively. In the available literature no case of contact dermatitis due to this substance was found. A case of atopic dermatitis due to goat hair protein has been reported by Rowe and Rogers.[1] The case herein reported is one of contact dermatitis in which positive patch tests were obtained to the oil extracted from goat hair, and favorable results were observed following treatment with a solution of this oil.

CASE REPORT

Mrs. W. M.,† aged forty-eight years, white female, school-teacher, was first seen Nov. 10, 1934. complaining of an itching eruption on her face, arms, and legs, of twenty years' duration. It was thought to be a contact dermatitis, but the cause was not found. She was not seen again until Feb. 16, 1935, when the same type of dermatitis was noted in the same areas. This consisted of many excoriations and tiny patches of dermatitis. Exacerbations had occurred frequently since onset, and no causative agent had been found. There was no seasonal variation.

There was no family history of allergy, but the patient had had several attacks of urticaria as a child. Other past history and general examinations were irrelevant.

Attacks had occurred both at home and while traveling. Patch tests were done with many of the common contact excitants, including orris root oil, shampoo oil, Palmolive soap, dwarf and giant ragweed, head of a match, wave set material, thrasher dust oil, house dust oil, hair from her pet cat, and pieces of material from her clothing. All were negative, with the exception of house dust oil and a piece of a wool dress, both of which showed a mild erythema after forty-eight hours (the house dust probably contains a small amount of mohair). Patch tests with pieces of black and white moiré silk both showed erythema and a few tiny vesicles after forty-eight hours. They were mild reactions. (Moiré silk contains some goat hair.) About this time the patient suggested mohair, as she noted a flare-up after a nap on her lounge. As mohair is made of goat hair, a bit of this material was obtained from a large wool company in St. Louis. The material from the lounge and the goat hair both showed a definite positive patch test with vesiculation, erythema, pruritis, and burning, after forty-eight hours. These tests were done on the flexor surface of the forearm. A larger amount of undyed goat hair was obtained from many bundles of this material. After washing with water, an acetone extract was made with a comparatively large yield of oil. A patch test with this oil was positive. A 1 per cent solution of the goat hair oil was prepared in almond oil and

*Studies, observations and reports from The Barnard Free Skin and Cancer Hospital, and the School of Medicine, Washington University, Department of Dermatology.

†From the private practice of Dr. M. F. Engman, Sr., through whose courtesy this case is reported.

sterilized by passing through the Seitz filter. Injections deep in the gluteal muscle were begun April 13, 1935, with 0.5 c.c. of this solution. The second injection of 1 c.c., given one week later, seemed to cause a flare-up of her condition; so several more 0.5 c.c. injections at weekly intervals were given. On May 18, 1935, 1 c.c. was given with no ill effects. These were continued until twelve injections had been given, and she was markedly improved. After a three-week interval, injections of a 2 per cent solution were begun, and nine 1 c.c. doses of this were given. On Sept. 28, 1935, it was noted that she had been completely free of the eruption for a period of three months. At this time a patch test with the goat hair oil was applied to her forearm. After forty-eight hours a mild erythema was noted with slight pruritis. The reaction was much less than that noted before the treatment. Injections were discontinued at this time, and the patient has remained well up to this writing. It is the first time she has been entirely free of eruption for several years.

COMMENT

Distributors of goat hair advise me that it is used for many purposes including mohair in seat covers of automobiles, trains, furniture, etc., draperies, bedspreads, rugs, and in clothing of many descriptions. It is commonly blended with wool, silk, or cotton in varying amounts, depending on the predominating character desired.

The widespread commercial use of goat hair and the infrequent reference to it in the literature, prompt me to submit this report. The marked improvement following specific treatment with the diluted oil is also a very significant observation.

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Society Proceedings

COMBINED MEETING OF THE ASSOCIATION FOR THE STUDY OF ALLERGY AND THE SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS

ATLANTIC CITY, N. J., JUNE 10 AND 11, 1935

Observations on Acne and Allergy. T. D. CUNNINGHAM, M.D., and J. C. MENDENHALL, M.D., Denver, Colo. (Abstract.)

The cause or causes of acne are still under discussion. Many authors[1-5] have made observations relative to foods and this condition. Bloch[6] found acne in 59.6 per cent of 2,136 girls, and in 68.5 per cent of 2,055 boys between the ages of six and eighteen years.

In this study of 42 consecutive patients with acneiform lesion, all over thirteen years of age, most of the common types of this condition are found. Each patient was tested by the scratch method to all foods. Many patients had had x-ray treatment previously. Patients tested for time interval after ingestion of food to which they were sensitive, required twenty-four hours before the lesion would appear. The first signs of a lesion were itching, then formation of a nodule under the skin. This nodule would sometimes recede if the offending protein was removed from the diet. If ingestion of such a protein continued, however, the lesion would go on to so-called acneiform lesions. Lesions once well established required from four days to a week to disappear—deep burrowing pustular lesions drained spontaneously when all the offending foods were removed from the diet.

A history of acne seems as good a clue to allergy in the family as a history of hay fever, migraine, or asthma.

Not all cases of acne clear on removal of foods from the diet. Some females will have a recurrence of lesions just before menstruation. These can be greatly helped by administrations of ovarian extract. Others require ovarian extract to clear the skin although not near the menstrual period.

The acneiform lesion can be produced by the subcutaneous administration of wheat extracts in patients sensitive to this protein; hence intracutaneous testing may increase the acne rather than diminish it.

In certain cases it was observed that foods which cause acne do not produce indigestion or other allergic phenomenon. This suggests that protein sensitization has specific localization.

Patients in whom the skin did not clear after removal of foods which were positive on the first test were frequently retested and

other foods were then removed from the diet. Also, it was observed that patients change their sensitization from time to time and require repeated skin tests. This varies with the individual patient.

The results in this series of 42 cases are as follows: All patients were tested with the same 165 foods, and every patient was definitely sensitive to some of the foods. The least number of foods reacting on a patient was 16 and the largest number 79.

The following are the patients' own estimates of their improvement:

19 patients (51 per cent) received from 90 to 100 per cent relief.
5 patients (13 per cent) received from 70 to 90 per cent relief.
3 patients (8 per cent) received from 50 to 70 per cent relief.
5 patients (13 per cent) received from 10 to 50 per cent relief.
5 patients (13 per cent) were not benefited at all.

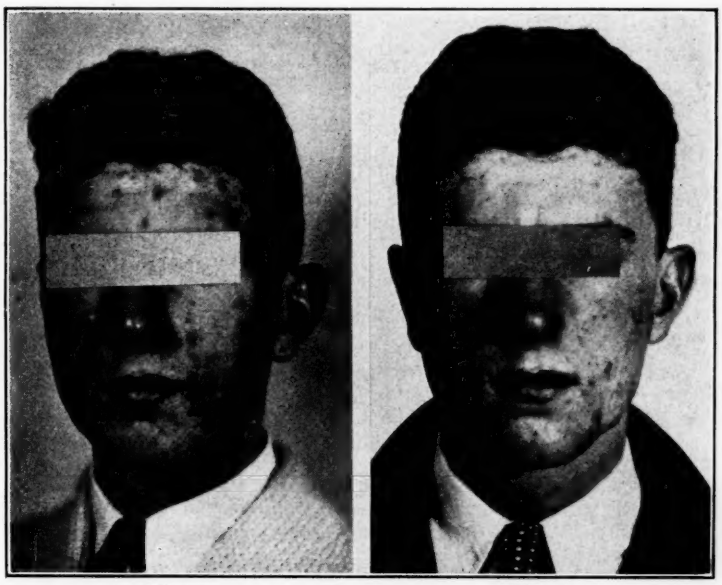

Fig. 1. Fig. 2.

Fig. 1.—Photograph of patient before going on exclusion diet (March 28, 1934).
Fig. 2.—Same patient, after ten months of diet, Dec. 13, 1934. No active lesions, only scars.

These figures are not unlike the percentage of relief obtained when the treatment of hay fever with pollen extracts was first used.

The foods which reacted more than others were spinach (25 times), pork (18 times), and potato (18 times).

Attempts were made to desensitize two patients both sensitive to wheat. In each the acne lesions were reproduced with the injection of the wheat extract. One patient was benefited considerably. Desensitization has not been thoroughly tried.

Patch tests on three patients for a limited number of foods were negative after twenty-four hours.

SUMMARY

1. Practically all patients with acne are sensitive to food proteins.

2. The percentage of acne in the population is practically the same as the percentage of allergic individuals in a community.

3. A history of acne seems a sound basis on which to judge allergy in a family or a patient.

4. Apparently other factors as endocrine disturbances can and do produce acne in a small group of patients.

5. Repeated tests for sensitization are mandatory in any allergic condition for the best results, and especially in cases of acne.

6. The majority of patients with acne (75 per cent) received from 50 to 100 per cent relief by avoiding foods to which they reacted.

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DISCUSSION

DR. SULZBERGER.—What Dr. Cunningham has just told us seems to me almost too good to be true. I suppose, year in and year out, in practice and in my various clinics and in hospitals, I see daily a number of acne vulgaris cases perhaps approximating that of the entire series here reported. It has been my impression that if specific food hypersensitivity plays any rôle in acne vulgaris, it must be the great exception. Of course I have not carefully skin tested or dieted all these patients, but I have seen a fairly large number in which both had been done by others. I know of no cases in which the elimination of foods or placing the patient on special diets has, without other measures, brought about a striking improvement or cure. I have seen many patients who have been skin tested because they have had concomitant asthma or hay fever and who were put on strict elimination diets, but in spite of these eliminations the acne has persisted.

The point is, of course, that if foods are a factor (and Dr. Cleveland White, Dr. Stokes, and Dr. Cunningham and many others have voiced the impression that foods may be a factor), they are certainly only a secondary factor, I might even say an insignificant factor, in the production of the bulk of the cases of acne vulgaris. On the other hand, there is a clear case against the endocrine mechanism as being the basis in the production of acne vulgaris. It is a disease of puberty. From the practical viewpoint, no person before the beginning of the first awakening of puberty ever has true and typical acne vulgaris. No eunuch has acne vulgaris, no matter what foods he eats, or what sensitivity he may have. No senile person has acne vulgaris. It is a disease which begins with, and ceases after, the gonad activity of

the human being. It is closely linked with the menses in women. Almost one hundred per cent of young girls with acne vulgaris have exacerbations of their acne one to two days preceding the menses. Furthermore, acne vulgaris is influenced by pregnancy and adrenal tumors and other endocrine upsets. On the other hand, there is no doubt that acne vulgaris is a result of irritation of the pilosebaceous apparatus. If we try to link this fact with the endocrine aspects, we must conclude that acne vulgaris may be due to hyperstimulation, i.e., irritation of the pilosebaceous apparatus by hormones. We know that the hormones produced at puberty are normally stimulators of the hair, of the follicles, and of the sebaceous glands; for the hair changes, the beard begins to appear, the terminal hairs begin to grow, and the secretion of sebum increases. This pilosebaceous apparatus is exactly the apparatus in which at this time the acne lesions occur.

It is interesting to note a further fact; namely, that not only acne vulgaris but also baldness (which is, in my opinion, part of the same disease of the hair and its appendages) are of familial occurrence and are often associated. Three of my brothers and one sister had severe acne. My father was bald when he was twenty, and I was bald when I was twenty years old. These points of view have been set forth by Rostenberg, Sher and myself in a recent article in the *New York Medical Journal and Record.*

All in all, I should say that there may be isolated instances of acne vulgaris in which food plays a clinically significant rôle, but I am afraid they are in the great minority. I therefore believe that the dietary approach to acne vulgaris is preordained to fail in most cases.

Dr. Albert H. Rowe.—I have been studying this question of acne from the point of view of food allergy for a good many years. In my monograph, I commented on the disappearance of acne in one patient who had a severe type of asthma or perennial hay fever; and the acne, much to my surprise, disappeared without any local treatment at all after the foods to which this patient was sensitive were eliminated. Since that time, Dr. Cleveland White of Chicago has profited by the observation which I made at that time, and has published a number of cases of definite relief obtained by the elimination of specific foods. I have gone on with my work in the last four or five years, and I am sure I have seen a number of cases of acne that have been definitely relieved by the sole elimination of foods to which the patients were apparently sensitive.

Some of these patients showed acne as a single evidence of food sensitization; others had other concomitant manifestations of allergy along with the acne.

I am certain from the experience I have had in the attempt to relieve many of these patients with acne that food sensitization is not solely the cause of acne. The type Dr. Sulzberger has mentioned is the predominating type in adolescence. I likewise believe that food sensitization should be taken into consideration as one of the common causes of acne in adolescence and in young adults, and even possibly before adolescence occurs.

As in all of my work, I do not depend on the skin reaction for the determination of skin sensitization entirely. I routinely do the scratch test; I obtain what information I can from it, and then I modify the

elimination diet according to the definite reactions that I have obtained, realizing, as was shown by Dr. Rackemann, that all positive skin tests do not indicate clinical sensitization. I believe it is just as important to use diet trials to determine the value of a positive skin test as it is to use a trial diet to determine the value of negative skin reactions.

There is an interesting case I have in San Francisco of a young woman who had had much dermatologic treatment for many years. I put her on an elimination diet. She had had limited x-ray and all kinds of local therapy. Within two or three weeks her acne was very much relieved, and within two or three months it had disappeared. It was interesting that the mother had had an acne which had disappeared when she was twenty-eight years old, in place of which she had had a constant flushing of her face, which was most annoying. Without telling me she took her daughter's diet, and found that the localized tendency to flushing, which I believe was an equivalent of her acne, disappeared.

DR. C. MALONE STROUD.—In considering a problem of this sort, we should not step too far beyond the bounds of our specialty, especially when we consider that most of us are not trained in dermatology.

It has been my privilege to observe several patients with acne who were allergic. It was considered in each instance that allergy was merely a complicating factor. I mentioned such a case in a paper in 1931, in which a girl had been treated for acne for several years. She was not relieved until allergy was taken into consideration. She was found to be sensitive to orris. When the offending allergen was removed, dermatologic treatment resulted in rapid improvement.

I agree thoroughly with Dr. Sulzberger and feel that we should not be over enthusiastic. I believe that food allergy is a rare complication of acne and that it rarely, if at all, is the sole causative factor. In studying acne, we should work in conjunction with experienced dermatologists.

DR. VAUGHAN.—From my own experience I am confident that allergy plays a part in a certain proportion of cases of acne. I have not found the percentages as high as Dr. Cunningham has.

We have had one interesting case, too recent to report formally, but I am going to mention it because of its interest in this discussion: A woman who, when she eats beef, promptly vomits and gets no acne. When she eats eggs, she does not vomit but a few hours later develops an acute colitis, a diarrhea, and the next day breaks out with pustules on the face. That is true of a large number of foods. If she gets rid of it, she does not get acne. If she does not, she gets an acne type of dermatitis, with big pustules always full of *Staphylococcus aureus.*

We tested her a year and one-half ago and found her tremendously sensitive by skin test to a large number of foods. We put her on allergic avoidance, based on the skin test, and she got no better. A year later she came in again. We did leukopenic index studies on her and found her sensitive to a number of foods. There were many foods, about fifteen, that she could eat with impunity as far as we could determine by the leukopenic index. This regime has not gone long enough, only a month, but she is very much better. The inter-

esting part of it is that of those fifteen foods that apparently she can eat on the basis of the leukopenic index and is eating, fourteen gave positive skin reactions. Therefore, I would suggest to Dr. Cunningham that on his no-result cases, he might be interested in trying leukopenic index studies.

Dr. Abraham Walzer.—We have to look at this question from its dermatologic angle also. There are many types of acne. Bromide acne, for example, has very little connection with acne vulgaris, from its clinical, histopathologic, or other aspects.

Acne vulgaris means that the acne begins with a comedo. Therefore, according to Dr. Cunningham, the comedo should be considered allergic, which I do not think will be accepted. A comedo is not dirt, but a hyperkeratosis of the mouth of the follicle, plus a solidification of the secreted oil. This eventually occludes the mouth of the follicle, with the formation of the papule. Secondary infection may set in, and pustule may superimpose on the papule.

As I stated before, there are a number of types of acne. Dr. Cunningham's case shows too many deep-seated scars which is not what is ordinarily seen in acne vulgaris. It appears to be a case of acne tuberculid.

Acne vulgaris is a disease of puberty, beginning and ending any time between about twelve and thirty years. It is in all probability hereditary, in the sense that the type of skin which induces acne at this period of development is hereditary. It might be an endocrine disturbance as suggested by Dr. Sulzberger, but its familial occurrence is too frequent to be disregarded.

In closing I want to say that acne vulgaris according to its clinical and histopathologic appearances is not the type of disease one usually associates with food allergies, and I cannot see how it can possibly be grouped under such head.

Dr. T. D. Cunningham.—In the case I showed, the patient was said by two of the best skin men to have acne vulgaris. I am not in position to quarrel about terms. These cases are people who came in the office, all patients in private practice, with lesions on their faces that you ordinarily call acne. We did not go into detailed questioning, did not have a dermatologist see every one. In the more severe cases, the patients had been to a dermatologist.

The question of vitamins, I think, is very important, and you will certainly clear up a small percentage of patients by giving them viosterol, or any one of the vitamins. If you believe the newspapers, yeast will also clear up a certain percentage.

Of course, I do not see the large number of acne cases that the dermatologists do, but I raise the question, why not give the acne patients a chance and find out whether they are sensitive before they are given x-ray treatment? I believe the patients should have the opportunity of having the foods removed from the diet, rather than severe x-ray treatments.

Unquestionably the endocrines are a big factor, and I raise the question as to how big a factor the endocrines are in allergy; whether allergy is not an endocrine disturbance and the acne a form of allergy based on endocrine disturbance.

I did not come here to fight for my opinion of acne's being allergic. I reported these cases because they are interesting. You cannot treat them as you do hay fever or asthma, because if you do, you will fail every time. You have to sit down with these patients and have them bring in a list of the things they have eaten. I do not believe you can get the results nor the cooperation in a clinic that you can get in your private practice. Most of these patients do not know what they are eating. When you can reproduce a whole series of severe acne lesions by the introduction under the skin of a solution of 1:20,000 wheat (it takes such a small amount to produce acne lesions), it suggests allergy as a factor.

What I do with these people is skin test them repeatedly in order to find out what they are sensitive to, as they change their sensitization very quickly in two or three weeks. They may become sensitive to some of the foods you put them on. Those who have the milder acnes will yield more quickly than the more severe. If you work hard with your private patients, you will find it will well repay you in the results obtained.

Annual Review

ALLERGY IN DERMATOLOGY

A Discussion of Recent Contributions and of Their Relationship to Earlier Dermato-Immunologic Studies

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IT IS the purpose of the present review to mention and to discuss critically certain selected recent contributions to dermatologic allergy, and the relationship of these newer contributions to the older work in this field.

In the discussion, free rein will be given to personal opinions and reactions, for I believe that a strictly uncritical presentation would be not only uninteresting, but repetitious; as a great part of the literature considered has perforce already appeared in abstract form in various American journals.

The many dermatologic manifestations of allergy may be divided somewhat categorically as follows:

1. Diseases of the skin which are based upon allergic alterations of response, or in which allergic alterations play a demonstrable part; and the skin test and other experimental reactions in these skin diseases.
2. Allergic skin reactions (for example, to skin tests) in conditions which are not primarily diseases of the skin.
3. Allergic (immunologic) manifestations, mechanisms, and processes of the skin; and the influences such skin phenomena may exert upon the entire organism, or upon other systems, or upon individual organs.

ALLERGY IN DISEASES OF THE SKIN

Eczematous Dermatitis of Allergic Origin (Contact Dermatitis), and Its Differentiation From Atopic Dermatitis (Disseminate Neurodermatitis)

Unfortunately, it is still necessary today to define the precise manner in which one is employing the term allergy, and still more necessary to be exact in one's usage of the term eczematous.

The definition of the word allergy has, of late years, been much distorted and much abused; and the term eczema has never been clearly defined. So that even those considered to be authorities hold divided opinions as to the exact meaning of the designation "allergic eczema."

It is, therefore, gratifying to note that, in the last year or so, there has been a decided movement toward finally accepting the definition of allergy as *a specifically altered state produced by previous exposure,*

and made manifest by subsequent exposure to the same (or some closely related) substance. This definition is the one most closely adhering to the original concept of von Pirquet[1] who coined the word allergy in 1906. This time-honored definition is still the most logical and the one constantly employed by the greatest authorities in immunology and dermatology, and the only one which is, in my opinion, nonprejudicial and precise.

Rackemann,[2] in his recent excellent summary, unequivocally adopts this definition, and thus expresses his agreement with Landsteiner, Schick, Coca, and many other authorities. On the other hand, the definitions and new terms discussed and championed by Urbach and his collaborators seem to me to be not only a step backward, but also clearly untenable. In fact, Urbach and Wolfram,[3, 4] who postulate the demonstration of responsible antibodies to justify the application of the term allergy, immediately contradict themselves by citing as classic examples of allergy such conditions as Bloch's primrose sensitization, in which no antibodies have ever been demonstrated and in which the responsibility of antibodies thus remains the sheerest hypothesis.

Such contradictions are necessarily a common occurrence in the publications of those who define allergy as an antigen-antibody reaction; for it is immediately apparent that when they demand the proved responsibility of antibodies as a *conditio sine qua non* of allergy, they exclude from allergy the most classic forms of the original allergic sensitizations and immunizations. The definition of allergy as an antigen-antibody reaction automatically excludes from allergy (for the present, at least) the specifically altered states in tuberculosis and in tuberculin reaction, in syphilis and in luetin reaction, in fungus diseases, and in trichophytin and oidiomycin reaction; in smallpox and in vaccinia reaction; in drug sensitizations; in contact eczema, and in eczematous plant sensitizations—for in these and in many other accepted allergic, specifically altered states, no responsible antibodies are regularly demonstrable by means of present methods.

Most of the examples I have mentioned not only belong to the classic forms of allergy but are indeed among the very ones cited as prototypes of allergic changes by von Pirquet. Von Pirquet goes to some pains to show that he has coined his new word—allergy—to cover all states of specifically altered "capacity to react" (Reaktionsfähigkeit). Fortunately, von Pirquet is most precise and leaves no room for uncertainty as to his reasons for the inclusions and exclusions under his new designation. He says that he is impelled to the formation of the word allergy by the necessity for a term which is nonprejudicial and which includes both the closely related and often coupled, but nevertheless diametrically opposed phenomena of specific immunization and sensitization. Von Pirquet expressly and emphatically says that al-

lergy is to apply to all specifically acquired states of hypersensitivity, of hyposensitivity, or of immunity, regardless of whether they be caused by living or by nonliving agents, and regardless of whether these states be accompanied by demonstrable antibodies, or whether no antibodies of any kind be found.[1]

In regard to the term eczema, a confusion of definitions has existed from the beginning; and, unfortunately, no reversion to original definition is possible here. The usage of the word eczema in describing various skin diseases is over 1,400 years old; and ever since Willan, in 1800, and Rayer, in 1836, dermatologic authorities have variously included almost every known inflammatory skin disease under the eczemas.

Neisser, Riehl, J. Jadassohn, Br. Bloch, and others have, however, clarified the modern concept through their development and elucidation of Hebra's eczema. Thus, a definite, morphologic, clinical, and histologic description of eczema has now been established. So that, while eczema undoubtedly still includes many varying, heterogeneous, and perhaps fundamentally and etiologically different skin diseases, we are at least able definitely to exclude many other forms and can assert that one or another more or less clearly characterized dermatologic entity is definitely not to be considered eczema.

Dermatologists have long recognized (certainly since Vidal—about 1886) that lichen simplex chronicus generalisatus is surely not a typical form of eczema. Vidal's lichen simplex chronicus generalisatus may be considered synonymous with the neurodermite diffuse *(a forme objective eczémato-lichenienne* of Brocq, and with the *prurigo diathèsique* of Besnier; and also synonymous with the generalized neurodermatitis or diffuse pruritus with lichenification of American and English authors.

It is, therefore, to be considered an important further advance that in the last few years the combined studies of dermatologists, pediatricians, and allergists (Rost, Moro, Woringer, Hill, and Sulzberger, Peck, Coca, etc.) have succeeded in further illuminating the picture of a certain form of neurodermatitis; so that this form now begins to emerge as a clearly circumscribed disease entity. It is certainly distinct from contact eczema, and also fairly distinct from other forms of lichenification such as circumscribed neurodermatitis, or *lichen circumscriptus* of Vidal. The disease, formerly usually called a generalized neurodermatitis, has thus recently become more sharply delineated, and has been designated as late exudative eczematoid by Rost; while the last years' work has brought about an increasing general agreement that this distinctly atopic dermatitis, including certain infantile eczemas, forms a fairly typical and well-characterized disease entity—regardless of one's opinion as to mechanism, pathogenesis, or etiology—and there is now not only dermatologic but general compre-

hension that this disease entity is separate and distinct from the still protean and diverse, but nevertheless clinically and histologically identifiable true or dermatologic eczema. As previously mentioned this separation of atopic dermatitis (or disseminate neurodermitis) from eczema has long been axiomatic with dermatologists (Vidal, Brocq, J. Jadassohn, Rost, etc.), but I believe that the recent contributions of such allergists as Coca[5] and Rackemann,[2] and of pediatricians such as Hill,[6] have for the first time succeeded in convincing their respective colleagues of the necessity for the separation of this established atopic entity from eczema of the nonatopic contact type.

On the other hand, many of the other varied forms of eczema cannot, as yet, be sharply differentiated from one another. For example, the nummular forms, the so-called parasitic or orbicular eczemas—while certainly in most instances different from eczema of classic allergic contact type, must still, on purely morphologic, clinical and histologic grounds, be included in the eczema group. The very latest articles of Adamson[7] and of Ingram[8] have, to say the least, been of little help toward clarification and differentiation.

For the many reasons cited, I believe that the term allergic eczema can today comprise only dermatitides possessing the clinical and histologic characteristics of eczema, and proved to be due to a specifically acquired state of hypersensitivity.

In classic allergic eczema (contact eczema) the most important studies of the year have been devoted to the mechanism and nature of, and to the factors which influence the patch test responses. Miescher[9] has shown that, as has always been recognized, there is a clinical and histologic picture characteristic of eczematous skin reactions. He has further demonstrated that this picture can be produced, not only in allergic reactions in contact eczema (i.e., eczematous responses due to sensitization to simple contact substances), but that the same morphologic reaction also occurs regularly in eczematous skin responses to primary irritants, as well as in truly eczematous reactions not only to simple compounds but also to fungous and bacterial products (such as the patch test responses to oidiomycin, first described by Ramel, and the patch test reactions to trichophytin, which George Lewis and I[10] have reported).

Burkhardt[11] reports the important fact that those eczema patients who have been exposed in their occupations to the injurious effect of alkali (for example, plasterers, galvanizers, laundresses) all exhibit a definitely lowered threshold of resistance to alkali. According to this author, normal skins possess, as an inherent function of the epidermal cells, the ability to neutralize alkali solutions at a certain rate. In the examined eczema patients who had been exposed to alkali, this function was impaired; and individuals with lowered alkali resistance seem

then to be prone to true, eczematous-type, allergic sensitization to substances other than alkali. This, in Burkhardt's opinion, may be one of the causes, or so-called predisposing factors, contributing toward eczematous sensitization and allergic hypersensitivity in occupational eczemas due to cement, nickel, turpentine, etc.

This study is obviously important, as it represents the first scientific approach toward the understanding of an individual, predisposing (constitutional) skin factor underlying susceptibility to eczematous sensitization.

Mahler[12] demonstrated that the flexor surfaces of the extremities were more sensitive than the extensors; and that the upper part of the body was more sensitive to patch tests than the lower half. He also demonstrated that neither high fever nor profuse sweating influenced allergic patch test reactions, although patients with high temperatures were more sensitive to nonspecific primary irritants. This work is of importance in the study of certain compensation cases in which the patch test results might otherwise have been supposed to be influenced by the perspiration gathering under the impermeable substance covering the test site.

Wedroff and Dolgoff[13] perfected a technic for quantitative skin testing by the drop method. The substance in solutions of varying concentrations were applied as single drops. Each substance was applied in concentrations varying from 3 per cent to 25 per cent to the uninjured skin of 150 eczema patients, and to normal controls. Eighty per cent of the eczema patients reacted to the 5 per cent to 10 per cent solutions; whereas 80 per cent of the normal persons responded only to concentrations of from 15 per cent to 20 per cent. The authors state that the question thus arises as to whether the polyvalent hypersensitivity of the majority of eczema patients may not be due to increased permeability of the skin.

These experiments confirm the original work of Bloch and Jaeger, showing that eczema patients tend to polyvalent sensitization of eczematous type—a concept which has become of great importance in the study of contact eczema, and particularly in the adjudication of compensation cases.

Wedroff and Dolgoff, in a second paper,[14] also demonstrated, by means of the drop method, that 50 out of 72 eczematous individuals could be sensitized experimentally by one application of a 10 per cent solution of dinitrochlorbenzol in acetone. Normal persons required solutions up to 30 per cent to achieve sensitization. The sensitivity in the individuals thus sensitized was sometimes more than 100,000 times as great as the original degree.

With this method, the authors were able to determine the incubation period for allergic eczematous sensitization, and found it to be from

eight to twenty-four days, which roughly coincides with the incubation period for butesin picrate sensitizations, as determined by Wise and me.

Straus[15] was able to sensitize infants by the application of an acetone solution of poison ivy oil directly to the skin. The sensitization was most successful by external application, less successful by intracutaneous injection, and could not be achieved by oral administration.

This work confirms the early work of Spain and Cooke in man, and has some relationship to the animal sensitizations of Frank A. Simon, Margaret Simon and Dienes with poison ivy, and of Brunsting and Bailey; and, above all, shows the general applicability of the laws established in the original sensitizations of Bloch, and of Bloch and Steiner-Wourlisch with primrose allergen. The last-named authors found that percutaneous application proved to be the most efficacious manner of specifically sensitizing the skin, both in animals and in man. This also coincides with many previous dermatologic observations, such as those of Bloch and W. Jadassohn, and of Sulzberger, with fungi; with those of Martenstein with tubercle bacilli; and with those of W. Frei, R. L. Mayer and mine with paraphenylendiamin and neoarsphenamine.

Brunsting and Anderson[16a] report important observations with patch tests, employing the plant oils in 18 cases of ragweed dermatitis. These authors showed that there was not infrequently a group sensitization, not only to the various ragweeds and burweed marsh elder, but also to turpentine and especially to pyrethrum.

I, too, have been struck by this association of positive patch tests to pyrethrum, ragweed oil, and turpentine, and can corroborate Brunsting and Anderson's findings. It is little short of fascinating to recall that scratch or intracutaneous tests with the protein fractions of these plants bring to light a similar grouping of urticarial reactions to the water soluble components of the ragweeds and of pyrethrum (Feinberg[17]).

Engman, Moore, and Kile[18] studied the nature of the plant oil allergen, which Brown, Milford, and Coca[19] first showed to be the active principle in the production of certain allergic eczematous pollen reactions of contact type. They report that the specific excitant is contained in the unsaponifiable fraction of the oil.

A possibly significant observation is that of Stroud,[20] who showed that the oil extracted from house dust produced positive patch test reactions in certain patients suffering from allergic dermatitis of the contact type.

Stroud's work certainly merits weighty consideration and further study, for it suggests the possibility that cases of contact eczema, heretofore of obscure causation, may actually be due, in some instances, to external contact with common air-borne environmental allergens. The genesis of these cases would thus be analogous to that in the well-

known contact dermatitis from pollen oils, with the important difference that nonseasonal and ever present substances would here act as causes and thus increase the difficulty of etiologic diagnosis and of preventing exposure. Of course, this type of contact dermatitis produced by air-borne allergens must be sharply distinguished from atopic dermatitis of the noncontact type, which *may* be produced by the inhalation of air-borne substances (Vaughan and I,[21] Hill,[6] Taub and Zakon,[22] Figley and Parkhurst[23]); and also from atopic dermatitis which in some cases may be due even to contact in those instances in which there is transepidermal penetration and absorption of the wheal-eliciting atopens. The patch test reaction due to feathers, reported by Peck and Salomon[24a] in infantile eczema may, in my opinion, in some instances be an atopic vascular reaction due to such transepidermal penetration of the atopen.

It seems important to study further the constituents of house dust oil. It may contain feather, cotton, horsehair, and wool oils, oils from floor polishes, waxes, turpentine, oil-soluble dyes, or insecticides, cleansers, metal salts, and countless other possible known and as yet unknown elicitors of contact eczema.

In the year's literature there are numerous reports demonstrating the practical value of the patch test. It is not surprising, therefore, that the employment of this test is revolutionizing the study of occupational irritants and occupational dermatoses.

Two excellent articles by John Downing of Boston[25, 26] discuss industrial dermatoses from both medical and legal viewpoints, and do not fail to give due consideration to the importance of the allergic states of the skin. It may be recalled at this point that C. Guy Lane of Boston was one of the pioneers in the study of skin sensitizations in industry in the United States.

In Europe, following the fundamentally important monograph by R. L. Mayer,[27] Bering and Zitzke[28] have produced a volume on the modern aspects of the entire subject of occupational skin diseases.

In this country many investigators have succeeded in discovering numerous new substances which are proved capable of producing contact eczema, and many of these are mentioned in the "Queries and Minor Notes" of the *J. A. M. A.*, in the *Archives of Dermatology,* and in the summaries, such as those of Downing. Among the contributions dealing with industrial problems, I may mention one of Schwartz and Peck,[29] who demonstrated that the usual sensitizers in rubber and in adhesive plaster included various resins and pitches. Schwartz[30] has also submitted a short monograph on skin hazards in American industry. Both of these articles were made possible by the interest of the U. S. Public Health Service in the problems of skin sensitization in industry. The importance of these problems is apparent when one reflects that industrial skin disease costs this country over four million dollars yearly.

A great number of reports has been published, dealing with sensitization eczema produced by new or unusual substances. These substances include plants (gaillardia—Rostenberg, Jr., and Goode; camomile—Rowe); sodium morrhuate; perfumes, lipsticks, cosmetic creams, etc.; dyes, leather, shoe polish, flour bleaches, and so on, for a list too long to record here. In some instances, careful patch testing was able to bring to light the specific ingredient responsible for a sensitization in a dermatosis clinically resulting from contact with a complex mixture containing many substances. Thus, Baer[31] proved that his case of lipstick dermatitis was due to sensitization to the lipstick constituent methyl heptine carbonate; and that this substance is apparently a common sensitizer. The many positive reactions in Baer's control persons make one wonder whether the test concentrations of methyl heptine carbonate may not have approached the level of a primary irritating solution.

It may be stated that while all reports of new sensitizers are warranted when brief, the general laws governing the contact-eczema type of sensitization are certainly more important than the addition of new specific allergens to the existing list. Recent investigators have continued to emphasize the fact that the patch test, like other skin tests, while *specific* is not necessarily *diagnostic*. In other words, positive results cannot be regarded as proof absolute of the clinical significance of the substance tested; and negative results do not constitute exoneration. Each test must be evaluated in conjunction with all other factors, such as careful and exhaustive histories, opportunities for exposure, clinical and histologic appearance of the dermatosis, and particularly the results of elimination and renewed exposure.

It seems to me that the modern literature emphasizes these fundamental points and should continue to do so; and that this repeated emphasis will inevitably bring about a better and more general understanding of the clinical significance of positive and of negative patch test reactions, and thus liberate this valuable method from the adverse criticism which has frequently resulted from the lack of understanding of the natural limitations of all immunologic diagnostic procedures. As recently pointed out by Alexander,[32a] the immediate wheal reactions have been subjected to similar adverse criticism, and for similar reasons.

While specific desensitization of contact-type eczema has been the goal of many experiments, it must be admitted that the present methods are of no practical value in the majority of instances. In most cases, the avoidance of exposure is the only feasible procedure.

There are, however, many exceptions in which specific hyposensitization measures have proved to be of practical value, or have, experimentally at least, brought about a reduction of eczematous hypersensitivity. Among the early experiments in specific and nonspecific

desensitization as carried out both in man and in animals, I shall mention only the work of Samuel, Stein, and Schaer, of Klauder (nonspecific), of J. Jadassohn, of Strickler,[33] and of Spain and Cooke.[34] The three last named investigators carried out studies in desensitization to poison ivy; and it is due, in great measure, to this basic work that a method of specific hyposensitization has become of great practical value in both the prophylaxis and the treatment of contact dermatitis due to plant oils. Since the very earliest work of Strickler, Alderson, Sayer, and others, successful hyposensitizations with ivy oil have been reported.[34]

While the reviewer, together with Wise, reported (1930) the successful treatment and prophylaxis of ragweed dermatitis, the general usefulness of this method is the direct result of the later isolation of the oil excitant by Brown, Milford, and Coca[19] (see also Pascher and Sulzberger).

It may today be stated conservatively that contact dermatitis due to plant oils, such as the oils of ivy, ragweed, chrysanthemum, gaillardia (Rostenberg, Jr., and Goode), tulips (Caulfield, personal communication), may, in many instances, be benefited by specific hyposensitization; and that, furthermore, injections of the oil exert, in many cases, a certain prophylactic effect. There are, however, great variations in the results reported by the different authors. For example, Brunsting and Anderson[16a] were not particularly impressed with the results of specific hyposensitization in their ragweed cases.

While these differences in results are, as yet, inexplicable, I believe that they may be due to the fact that, as shown by Pascher and me, hyposensitization injections produce only a relative lowering of the degree of hypersensitivity. This lowering of sensitivity may be sufficient to prevent dermatitis under conditions in which the natural external exposure is slight or moderate; but not sufficient to prevent clinical manifestations under massive exposure, such as may have existed in Brunsting and Anderson's patients who were, in the majority, farmers in the midst of the ragweed district. (See in this connection the persistence of positive reactions to patch tests [i.e., to massive exposures] in hyposensitized individuals free from dermatitis under natural clinical [i.e., moderate] exposure. Spain and Cooke—ivy; Pascher and the reviewer—ragweed.)

However, this much can be said: specific hyposensitization measures by means of injection of plant oils have thus far been in general eminently more successful than have any hyposensitization measures attempted in contact dermatitis due to other excitants. The truth of this statement must be conceded, despite the many isolated reports of successful, specific hyposensitization in contact dermatitis due not to plant oils but to other substances, such as mercury (J. Jadassohn), formalin, phenyl mercuric iodide (Kesten and Laszlo[35]), ammonium

persulphate, etc. In spite of these reports, the inevitable conclusion is that specific hyposensitization has, as yet, no place in the general clinical management of contact dermatitis due to substances other than plant oils (see Questionnaire, Ref. 36). (It must be well understood that all the above remarks refer only to contact or true eczema, and have no bearing upon the eczematoid atopic dermatitis. I wish, however, to state in this parenthesis that my own few attempts at specific hyposensitization in atopic dermatitis have been uniformly disappointing.)

URTICARIA AND URTICARIAL REACTIONS

I consider it imperative once again to stress that, in my experience, there is no proof that the majority of cases of urticaria are produced by exposure to a specific allergen. It is true that isolated cases of acute urticaria are encountered in which the specific allergic mechanism can be proved beyond doubt. But the vast majority of cases of chronic urticaria and very many cases of acute urticaria must still be considered diseases of unknown etiology and obscure pathogenesis.

One of the most illuminating articles on this subject is that of Stokes, Kulchar, and Pillsbury.[37] It is impossible here to do justice to the wealth of observations and the exhaustive data assembled by those authors during ten years of study on 100 patients. I must content myself with quoting excerpts from the summary, as follows:

"... There was a marked familial and hereditary urticariogenic background in 60 per cent of the cases as compared with 25 per cent of the controls. There seemed to be a tendency toward familial distribution to the female side. ...

"Constipation was the one gastrointestinal symptom of major importance (55 per cent). ...

"Focal and intercurrent infections have undoubted etiologic importance, the precise weight of which is undetermined. Removal of a focus may or may not help. ..."

"Positive reactions to scratch tests for allergic conditions (complete in 28 cases) were obtained in 64 per cent of the cases. Atopic (multiple) sensitivity was observed. The presuppositions of the patient's history were more often negated than supported.

"The commonest allergic concomitants of urticaria were hay fever and vasomotor rhinitis. Other manifestations of the allergic state were rare. ..."

"The exclusion of substances to which the patient gave a positive reaction (scratch tests) and an elimination diet were conspicuously unsuccessful as therapeutic measures.*

"A comparison of two groups of published therapeutic results, different methods and emphasis being used, with our own, seems to support the view that attention to several factors in a case rather than to one alone increases the proportion of good results; that a variety of quite different methods, this hypothesis being taken into account, may be effective, and that in an unknown proportion of cases urticaria is self-cured. Dogmatic assertion as to sole causes is, therefore, to be deprecated."

*This corresponds strikingly with my own experience.

This paper gives so clear a picture that it should be read by all interested in urticaria. To my knowledge, no other contribution of recent years covers this subject so successfully, and I believe that I may therefore omit mention of the numerous other contributions presented in 1935.

Urticaria due to physical causes belongs to a special group. Bartels[38] describes a case of true heat urticaria. The eruption was not caused by sweat but was brought on by local and by general increase of temperature. The dermatosis appeared, regardless of whether the temperature was increased externally by baths or internally by means of injections producing hyperpyrexia. By painstaking, repeated application of heat, desensitization was achieved. Although attempts at passive transfer gave negative results, the author assumes that the heat urticaria was an allergic phenomenon. The main support for this viewpoint is the success of the desensitization procedure.

The fundamental work of W. W. Duke in this field is too well known to require detailed consideration here.

I do not believe that Bartels' contribution has conclusively proved that heat urticaria is allergic in nature. Sudden spontaneous cure is the rule in this affection.

Levine[39] has reviewed the literature and compiled the present views on the genesis of urticaria due to sensitivity to cold. This investigator performed an instructive experiment. He demonstrated that the tissue fluid, removed from a wheal produced by cold, elicited whealing in his cold-urticaria patient when injected into another skin site and without any further application of cold.

To me it seems that this does not constitute proof of the elaboration of a histamine-like substance in wheals due to cold. It merely shows that a substance can be found in the cold-wheal, to which the cold-sensitive individual reacts with wheal formation. This substance may be in the nature of an allergen or may be primarily urticariogenic as, for example, histamine is known to be.

Urticaria due to cold following measles in three sisters is the subject of a unique observation by Kobacher and Parkhurst.[40] There seems to be no doubt that the infection may have contributed to the production of this abnormal reaction to cold. The authors assume that the measles brought about a state in which there was an increased amount of H-substance in the skin.

I see no evidence to support this supposition. The reason for the connection between the measles and the cold urticaria seems for the present just as obscure as are the cause and genesis of cold urticaria itself; and as are the causes and mechanisms of so-called physical allergies in general.

In addition to these references to urticaria as such, several articles have appeared which seem to throw some light upon the production

of skin sensitivity of urticarial type, as demonstrated by wheal reactions to skin tests. The work of Colmes, Guild, and Rackemann,[41] of Rowe,[42] of Colmes,[43] of Alexander,[32a] and of Stevens[32b] may be summarized as demonstrating the following: Many of the urticarial skin reactions to tests are of no clinical significance. These reactions demonstrate merely that the individual has undergone a specific alteration in the reaction capacity of his superficial cutaneous vessels at that time and at that site, and now reacts with whealing to the local application of certain specific substances.

In studying 32 bakers, Colmes, Guild, and Rackemann[41] showed that 15 of these workers gave positive skin reactions to one or more environmental allergens (barley, wheat, etc.), thus demonstrating that the production of a wheal skin reaction was, in these instances, determined by exposure (sensitization). But of these 15 positive reactors, only one had clinical symptoms attributable to wheat. In other words, exposure tends to produce specific skin sensitization such as is brought to light by wheal reactions to skin tests. But for clinical symptoms to ensue, an additional, as yet unknown factor or factors must be present.

Rowe's work,[42] on the other hand, emphasizes once again the large number of negative skin tests to substances which ultimately can be proved to have etiologic significance. When foods are the factors concerned, the method of this proof is the elimination diet and reexposure.

These conclusions regarding the significance of wheal reactions are identical with those aforementioned in regard to the significance of patch tests, namely, that the results of skin tests are never proof absolute that a substance is or is not the actual cause of an existing condition. Skin test results are merely to a certain degree corroborative of other pertinent findings. This does not, by any means, detract from their usefulness, be they wheal reactions or patch test reactions. For the most firmly established immunologic diagnostic procedures—for example, serologic tests such as the Wassermann and the Widal—and in fact all other diagnostic material (e.g., bacteriologic, histologic, roentgenologic findings) must be evaluated in conjunction with all the other data before their results can be considered of conclusive diagnostic significance as regards the presenting clinical manifestations.

It is of interest to note that Colmes, Guild, and Rackemann showed that exposure to wheat produced urticarial sensitivity to skin test in a high percentage of nonatopic individuals; and to consider, in this connection, that wheat is one of the allergens which may be inhaled by bakers, in contrast to the exposure to ingested wheat which is fairly constant on the part of practically all individuals in the United States. This emphasizes once again the possible importance of the respiratory tract and of the inhalation route as a means of skin sen-

sitization, as was indicated in experiments by Vaughan and me,[21] and as Harkavy and I have pointed out in our work on the production of skin reactions in hypersensitivity to tobacco.

Chobot[44] found that 89 per cent of "allergic" children gave some degree of positive reaction to skin tests with tobacco extracts. This author concludes that tobacco acts as a primary irritant.

On the other hand, I am inclined to believe that Chobot's results may show that a high percentage of "allergic" children develops skin-test-type sensitivity to tobacco due perhaps to constant exposure to, and inhalation of, the perennially ubiquitous tobacco allergen. Chobot himself states that he has not brought conclusive proof of his contention that the tobacco allergen is a primary irritant substance, for it caused no contraction of the isolated uterine strip of guinea pigs. Until conclusive proof of the primary irritant nature of denicotinized tobacco allergen is brought, it would seem to me to be more logical to conclude that the skin reactions are due to sensitization and that Chobot's results parallel those of Colmes, Guild, and Rackemann, in that they demonstrate a high percentage of skin test reactions to strongly allergenic substances under conditions of more or less constant exposure by inhalation. In this connection it is to be recalled that Chobot was working with atopic children and employed an extract with high N content (0.1 mg. of nitrogen per cubic centimeter); while Colmes, Guild, and Rackemann studied an average group of adults with scratch tests. Furthermore, Harkavy and I both found that over 60 per cent of average normal adults do not react to tobacco skin tests. This finding, together with Chobot's negative Dale experiment, seems to contradict the assumption that the tobacco extracts contain primary irritant or primarily urticariogenic substances.

In studying the effect of various factors in the production of a skin refractory state to obligatory urticariogenic substances, Eliasz[45] comes to the conclusion that latent edema of the skin has a marked inhibitory action.

This finding will perhaps be shown to bear some relationship to the refractoriness to acceptance of passive transfer which Walzer and Bowman[46] demonstrated in the skin of a large percentage of atopic individuals. Walzer and Bowman's finding still remains an undoubtedly significant but still entirely unexplained phenomenon.

Many investigators have studied the chemical and physical nature of the fractions producing urticarial skin reactions. In the main, the work of Unger, Cromwell, and Moore,[47] of Black,[48] of Caulfeild,[54] and of Benjamins, van Dishoeck, and German[49] agrees with the earlier findings of Coca, and of W. Jadassohn,[50] namely, that substances eliciting typical and specific immediate-urticarial wheal reactions may be: (a) dialyzable, and (b) of nonprotein nature (e.g., carbohydrate, etc.). However, Cooke and Stull,[51] and Spain and Newell[52]

showed that in their cases the skin reaction seemed to depend upon the presence either of protein or at least upon the presence of phosphotungstic acid-precipitable nitrogen.

In considering this controversial subject, careful attention must be given to the now indisputable fact that what was until more or less recently considered a unit allergen is undoubtedly, in many instances, a complex mixture of numerous different substances, many of which are capable of eliciting specific skin test reactions. As Dakin and Dale showed in 1919, hen's egg albumen and duck's egg albumen each contain at least two separate antigens—one being a common, the other a species specific allergen. And W. Jadassohn[53] showed that such combinations of species specific and species nonspecific allergens are found in various fungi, in various other microorganisms *(Brucella abortus* and *Brucella mellitensis),* as well as in milk and in eggs of different species. Furthermore, Caulfeild[54] has demonstrated the complexity of common ragweed allergen; Osgood[55] of caddis fly allergen; Tuft,[56] that of horse dander; Simon,[57] that of certain mammalian sera; to mention only a few reports illustrating the complex nature of common allergens eliciting reactions to skin tests.

It cannot be surprising, therefore, that certain persons will respond with skin-test reactions to the dialyzable fractions, while others will not; that some will react strongly to allergens low in phosphotungstic acid-precipitable nitrogen, and others will not. One obvious interpretation is that this depends upon the particular constituent of the complex allergen mixture to which the individual's skin is sensitive. This, however, does not entirely explain the divergent opinions regarding the chemical nature of the fractions eliciting wheal reactions. Much work is necessary in this fundamental problem before the following can be decided: (a) what actual proportion of skin sensitivities is directed to protein fractions; and what proportion to the various nonprotein fractions, including carbohydates, etc.; and (b) whether nonprotein fractions, when unassociated with protein, can produce hypersensitivity, or whether such nonprotein constituents are, when alone, incapable of sensitizing, although proved to be elicitors of specific reactions in the already sensitized individuals? I do not believe that the possibility mentioned in my last question has been sufficiently considered, although it would seem that the work of Landsteiner with complex antigens, and the recent instructive work of Horsfall[58] with mixtures of formalin and serum, and the reports of Ratner and Gruehl[59] with mixtures of carbohydrates and protein, and of others—all indicate that, while nonprotein substances may elicit reactions in the sensitized, the presence of protein or at least of large molecular structures is necessary to produce hypersensitivity.

The entire difficult subject dealing with the nature of substances capable of producing specific urticarial immediate reactions in hyper-

sensitive skins is rendered baffling almost to the point of hopelessness by the recent discovery of Milton B. Cohen and collaborators.[60] Their revolutionary findings indicate that not only may a skin-test eliciting allergen be multiple and complex in nature, but that its power to produce skin reactions may be inconstant and variable. For Cohen and his collaborators have reported that extracts made from old cotton linters, even when these were preserved and aged in air-tight jars under sterile conditions, were infinitely stronger in eliciting wheal reactions than were extracts made from new and otherwise identical linters which had come from the same original bale. Moreover, this skin-test eliciting factor, newly and apparently spontaneously formed in aged linters, gave skin reactions paralleling those of house dust extract; and this cotton-linter allergen neutralized house dust reagins. Rackemann and Wagner[61] report that working with kapok they were able to parallel this astonishing finding of Cohen's group in cotton linters. They demonstrated a similar variation in skin tests to extracts of new and aged kapok. In Rackemann's brief remarks, no mention is made regarding the parallelism between house dust reactions and reactions to extracts of aged kapok. It seems to me not only that Cohen's discovery is one of the most striking in modern allergy, and not only of unpredictably great importance, both theoretically and practically; but that it may also hold the solution to the nature of the mysterious house dust excitant and may help clarify many other contradictions and puzzles in allergy. It may even serve to explain the previously discussed contradictory results of workers who have been studying the dialyzability and nondialyzability of skin-test producing factors. For, with the acceptance of Cohen's work, it obviously becomes possible that those investigators using fresh natural products would be employing materials with different skin test activity from those working with stored and aged substances; and different workers might thus achieve different skin test results with various chemical and physical fractions of their original material or its extracts.

INFANTILE ECZEMA

This disease will be discussed separately because it cannot be considered with certainty as a distinct and uniform entity belonging either to the true or contact eczemas, or to the atopic dermatitis group.

All recent studies seem to confirm the original dermatologic viewpoint that the bulk of infantile eczema consists, in the main, of three distinct diseases, as follows: (1) atopic dermatitis in infants; (2) contact dermatitis in infants; and (3) seborrheic dermatitis in infants.* It is, at present, unfortunately impossible to determine accurately

*There is probably a fourth group which is now being diagnosed simply as infantile eczema. This group consists of eczematous eruptions of various sorts, not classifiable under any of the three mentioned groups. (Mycotic eczemas—trichophytons, epidermophytons, monilia, etc.; other eczematous eruptions of unknown etiology.)

which group is of the greatest significance numerically. For the differential diagnosis between these groups is often extremely difficult; it must frequently be made *ex juvantibus;* and, in many cases, it is utterly impossible. Furthermore, the divergent results with patch tests with feathers, as reported by Peck and Salomon[24a] and by Hill,[62] suggest that different clinical groups (New York and Boston) may contain varying and different proportions of the above-mentioned types of infantile eczema.

Nevertheless, the earlier work of Rost on early exudative eczematoid, of Moro, and of others, and the many recent contributions for example of Peck[24b] and of Hill in the United States, and of Woringer[63, 64] and of Péhu and Woringer[65] in Europe, confirm the necessity for the division of the bulk of infantile eczema into the three distinct dermatologic entities of atopic dermatitis, contact dermatitis, and seborrheic dermatitis.

The last-named authors considered principally the atopic group. They call attention to the following well-known observations which are confirmed in their own investigations: (1) From 50 per cent to 90 per cent of infantile eczemas show positive immediate wheal reactions to skin tests with egg white. (2) The more carefully one excludes infantile seborrheic dermatitis from the group tested, the higher the percentage of reactors to egg white. In a rigorously selected group, the positive reactions to egg white approach, but never quite reach, 100 per cent. (3) A large percentage of the positive reactors have Prausnitz-Küstner reagins, specific to egg white. (4) The skin reactions and the reagins may occur in infants who, since birth, were never exposed to egg white. (5) While in some cases the administration of egg white produces exacerbations of the eczema, in many others the infants can be exposed to egg white with impunity, in spite of marked skin-test reactions and in spite of high titre reagins to egg white; and, still more astonishing, in some of these cases, oral administration or injection of egg white leads to temporary remission in the severity of the eczema, or to complete but temporary disappearance of the eruption.

In discussing these observations, Woringer arrives inevitably at the conclusion expressed by Moro, by Hill and me,[66] and by others, namely, the positive skin reaction to egg white and the finding of reagins cannot be interpreted as indications that exposure to egg white is the cause, or even one of the causes, of the eczematous eruption under consideration. Both the origin and the interpretation of the specific skin test hypersensitivity and the specific circulating passive transference antibodies to egg white are still unknown. (Compare this with the general findings of positive skin tests and absence of symptoms, for example, as discussed by Colmes[43] and by Colmes, Guild, and Rackemann.[41]

To explain these mysteries, Woringer then evolves the ingenious hypothesis that the infantile eczema in these cases is due to the interaction of the specific antibodies and the skin tissues, without the necessity for the participation of the egg white allergen in eliciting such reactions.

While this hypothesis would undoubtedly help in explaining some hitherto inexplicable observations in the allergy of infantile atopic dermatitis, it is without parallel as regards any known form of immunologic antibody function. I therefore feel that until Woringer or others can bring proof of a harmful reaction taking place between antibody and tissues, without the presence of allergen, the hypothesis must be considered as lacking in plausibility and in factual support.

Woringer's assumption, however, seems to predicate that the antibodies concerned could in situ produce reactions with autogenous organ-specific antigens which were normal or abnormal constituents of the skin itself; and there do exist certain recent and highly stimulating observations indicating the presence of organ-specific antigens contained in the various tissues of many of the individual's own organs. It seems necessary to digress and to discuss here some of the studies in autogenous organ-specific allergens.

Organ-specific antigens in lens substance and perhaps in the brain and in other organs have long been known and have been repeatedly demonstrated. More recently, Burky[67] has carried out a series of enlightening experiments showing that rabbits may easily be skin sensitized to their own lens—and other organ-constituents (muscle) through the participation of microorganisms and their products (staphylococcus toxin)—or even of their products alone.

The work of Whitfield[68] on autosensitization in eczema suggests the possibility of such organ-specific antigens in the skin. Bizzozero[69] has most recently demonstrated that repeated intracutaneous injections of their own serum skin-sensitized 9 out of 25 persons in whom he carried out his experiment. The reaction was of the typical late-papular tuberculin-type. The histologic examination revealed tuberculoid structures, thus suggesting the conclusion that this was a specific and allergic alteration in the tissue reaction. (See discussion of tuberculoid structures as evidence of allergy in infectious processes.) In 2 of the sensitized subjects, the tuberculin-type sensitivity was preceded by the immediate-wheal form of reaction.

Rackemann and Simon[70] have noted such transitions from tuberculin-type sensitivity to wheal-type sensitivity in human sensitizations to guinea pig serum.

Tezner[71] discusses the genesis of these two types of reaction. The first observation in experimental skin sensitization of this type is the appearance of the tuberculin-type of twenty-four- to forty-eight-hour skin reaction. As the sensitization process continues, the immediate

wheal-type of sensitivity sometimes appears. Further treatment will then often succeed in reducing the tuberculin-type sensitivity.

The successive production of first the tuberculin-type and then of the wheal-type of skin sensitivity, followed by the reduction of the tuberculin-type of hypersensitivity as hyposensitization progresses, are all well-known dermatologic phenomena. They have frequently been described, and I have encountered these phenomena with great regularity in the course of hyposensitization through repeated intracutaneous injections of, for example, tuberculin, trichophytin, and oidiomycin. It is to be pointed out, however, that while the late tuberculin-type of reaction was regularly reduced, in my experience the urticarial immediate skin reaction, when once present, remained practically unchanged by the hyposensitization procedure.

It is to be stressed that the immediate wheal and flare reaction and the tuberculin-type of forty-eight-hour reaction are separate and distinct, often existing independently, and apparently due to entirely different forms of skin sensitivity.

The wheal reaction and the tuberculin-type reaction differ also in their histology. I shall, at a later point, consider in more detail the significance of the tuberculoid structures sometimes seen in the forty-eight-hour type of reaction, and shall call attention to their rôle in a certain form of allergic tissue response.

Regardless of these two types of reaction it is obviously possible that Bizzozero's demonstration of a sensitivity of the skin to products formed in autogenous serum may have some bearing upon Woringer's hypothesis in infantile eczema.

Quite aside from Woringer's hypothesis, his work on infantile eczema serves to confirm and to stress once again a point which I have previously mentioned in connection with the work of Colmes, Guild, and Rackemann, of Rowe, of Colmes, and of Alexander—namely, that neither the most strongly positive skin tests nor even the most unequivocal demonstration of the highest possible titre of specific reagins constitutes *proof* that the allergen in question has any causal relationship to the dermatosis under investigation. This point cannot be stressed too strongly, and must never be forgotten in connection with studies in such dermatoses as atopic dermatitis of infants, of children, and of adults, urticarias, and in all conditions in which skin tests and reagin findings are to be evaluated as to their significance in relation to the clinical condition.

DRUG ERUPTIONS

The allergic manifestations in the production of skin eruptions to drugs have continued to receive due attention in recent years. Drug hypersensitivities manifesting themselves in reactions of the truly

eczematous (J. Jadassohn) and of the immediate urticarial type may be accepted as based, in most instances, upon allergic sensitization.

In studies of such eczematous drug sensitizations due to butesin and to picric acid (butesin picrate), Wise and I[72] showed that there are three distinct periods to be considered in the production of the hypersensitivity:

(1) A period of refractoriness to sensitization, i.e., a period in which, despite exposure, the individual remains immune to sensitization, and during which no apparent process of sensitization of any kind is initiated. This period of refractoriness to sensitization may last for years or it may even be permanent in some individuals; or it may be of short duration (hours, days, or weeks) in others; or there may be a complete absence of refractoriness, so that the first exposure instigates an immediate sensitization process. This variability in the duration of refractoriness accounts for the variability in time required to elapse between first exposure and the appearance of disease manifestations in different, similarly and continually or sporadically, exposed individuals.

(2) A period of incubation of sensitivity, which seems to be fairly constant, and which varies between six days and two weeks. This period is analogous to the incubation period of serum sensitivity; and of allergic sensitivity in many infectious diseases (mycotic, tuberculous infections, etc.); in experimental arsphenamine sensitizations, primrose sensitizations, ivy sensitizations, ragweed sensitizations, etc. It represents the time elapsing between the sensitizing exposure or exposures and the development of sensitivity of sufficient degree to produce clinical manifestations or reactions to skin tests.

(3) A period for development of reaction, when tissues already sensitive are exposed to the specific allergen. This period is also fairly constant, usually occupying an interval of from twelve to forty-eight hours. It represents the time elapsing between the application of patch tests and the appearance of the macroscopically visible eczematous response of the previously sensitized skin; between the injection of tuberculin, trichophytin, etc., and the appearance of the typical papular twenty-four to forty-eight-hour reaction in individuals already sensitized to tuberculin, trichophytin, etc., by previous contact with the respective microorganisms and/or their products; between the intracutaneous injection of neoarsphenamine in a skin already specifically sensitized and the appearance of the visible tuberculin-type papule, etc.

Eruptions due to gold are receiving increasing attention. The purpuric and hemorrhagic forms are adequately discussed by Hudson[73]; and Eyermann[74a] reports a large number of cases showing the close

relationship between the drug purpuras, purpuras due to foods, and the classic Schönlein-Henoch's purpuras. (See also purpuras due to quinine and to ergot—Peshkin and Miller.[74b])

I am in agreement with Eyermann's conclusions concerning the possible relationship of these purpura groups, and concerning the probable allergic mechanism in a great number of hemorrhagic conditions.

Giauni[75] and Lichtenstein[76] present the evidence for the allergic nature of the different types of skin manifestations produced by gold, and conclude that the results of patch and intracutaneous tests demonstrate that a specific skin sensitization has occurred.

It is surely unnecessary to point out that the concept of the allergic nature of various arsenical and arsphenamine eruptions is supported not only by experiments similar to those mentioned above (Klauder, Stokes, and others), but also by experimental sensitizations in animals and in human beings (performed by Frei, by Nathan and Munk, by R. L. Mayer and the reviewer, and by others).

In addition to the severe erythematous, eczematous, and crustaceous arsphenamine eruptions, milder forms with less alarming prognosis not infrequently follow injection of arsphenamine. It is Milian who deserves credit for having called attention to certain morbilliform and sometimes scarlatiniform exanthems which appear about nine days after an arsphenamine injection, and which are now called erythema of the ninth day. Milian attributed these eruptions to the fact that a dormant agent, for example, the actual causal agent in measles or in scarlet fever, is awakened and activated by the arsphenamine, and that this results in the manifestation of the ninth-day erythema.

Milian points out that parasitotropic drugs may either (1) stimulate pathogenic agents (an effect which he terms biotropism), or (2) destroy pathogenic agents (an effect which is termed necrotropism).

Milian's discussion of these points is fascinating and instructive. Nevertheless, it cannot be accepted as proved that erythema of the ninth day is actually due to a stimulation of the dormant agents of measles and of scarlet fever. The erythema may also be explained as a simple sensitization to the drug administered, manifesting itself as a morbilliform or scarlatiniform drug eruption. Harther Keim[77] has submitted a detailed and objective analysis of Milian's arguments and of those favoring the alternate hypothesis of drug sensitization without the mediation of living agents, and gives cogent reasons for his adherence to the latter hypothesis.

While I incline to the concept that erythema of the ninth day is a drug eruption pure and simple, it must be admitted that the reason for the apparently lasting immunity to a similar recurrence, which

follows erythema of the ninth day, still awaits elucidation. For, in this respect, erythema of the ninth day differs from other morbilliform and scarlatiniform drug eruptions (for example, those regularly occurring after nirvanol). As is well known, in contrast to "E.9," the other morbilliform, scarlatiniform (nirvanol), as well as other forms of drug eruptions are wont to recur upon adequate reexposure to the drug.

Abramowitz[78] has recently compiled a masterly review of the evidence which so convincingly establishes the probable allergic nature of fixed drug eruptions in general, and of phenolphthalein eruptions in particular. He also reports original work demonstrating that neither phenol, phthalic anhydride, nor the various related derivatives or aromatic compounds produced the phenolphthalein eruption.

Because of their controversial and unsettled nature, I am avoiding detailed discussion of the transplant experiments in fixed drug eruptions in which Naegeli, de Quervain and Stalder[79] and others found that the hypersensitive area could be transferred from one site to another by the transposition of skin grafts; while Wise and I,[80] as well as Loveman,[81] reported diametrically opposite results. Knowles, Decker, and Kandle's[82] recently published experiments would seem to explain the divergent results as possibly due to the different intervals allowed to elapse between transplantation and the test drug administration. These authors' findings suggest that, if the drug be given early, the skin transplants react just as when in their original sites; while, if given at a later date, the skin transplant has assumed the reaction state of the site to which it has been transferred. These transplant experiments, whatever their result, deal merely with the question of the location of factors determining the production of local hypersensitivity, and with the question of whether this sensitivity is determined by the influences of underlying structures such as the nerves and the blood vessels. They do not touch upon the question of the allergic nature of drug eruptions.

The mass of material in favor of the allergic basis of certain drug eruptions has made it impossible to include specific mention and discussion of many papers. The overwhelming consensus, however, fully supports the original, brilliant concept of J. Jadassohn,[83] namely, that most forms of dermatitis medicamentosa are due to specific and allergic hypersensitivities. Those interested in this subject, if unable to obtain J. Jadassohn's epochal first contributions, will find pleasure and instruction in reading the clear and objective discussions together with the excellent bibliography to be found in the latest papers by Abramowitz,[84] Abramowitz and Noun,[85] and in the older chapters by R. L. Mayer,[86] and by W. Jadassohn.[87]

SKIN ALLERGY IN INFECTIOUS DISEASES

Skin Reactions and Immunologic Treatment, Exclusive of Trichophytin and Tuberculin Allergy

W. Jadassohn[88] has listed and discussed the infectious diseases in which immunologic skin reactions to microorganisms or to their products, or to virus, have been achieved. W. Jadassohn's list includes—in addition to the well-known specific skin alterations in tuberculosis, leprosy, and syphilis—the specific skin reactions which have been achieved in the following infectious diseases: frambesia, framboetin (Baermann); malaria (Herrmann and Lifschitz); leishmania-leishmanin (M. Jessner and Amster, and others); various fungous diseases, including those produced by trichophytons, epidermophytons, oidiomyces, blastomyces, sporotrichons, actinomyces, and coccioides immitis; variola, vaccinia; anthrax, bubonic plague, malleus (mallein—Nissl); undulant fever; soft chancre (Ito—Reenstierna, Dmelcos); lymphogranuloma inguinale [lymphopathia venerea] (Frei); typhoid fever (Wolff-Eisner, Large); rhinoscleroma (Soukup); hoof and mouth disease; diphtheria (Schick); scarlet fever (Schultz-Charlton, Dick); streptococcic and staphylococcic diseases; pneumococcic diseases; gonorrhea (Bruck, Peters, Herrold, Kasper, and others); typhus (exanthin—Fleck and Hescheles); dysentery (Brokman, Zoeller); erysipeloid (erysipeloidin—W. Jadassohn and Ju Wu Mu, Biberstein and Balbi); infestation with intestinal parasites (ascaris-oxyurus, etc. —Fülleborn, W. Jadassohn); diseases due to hypersensitivity to products of insects (Hecht and others).

While some of these studies have attained the utmost practical significance, it is true that by no means all these reactions are, as yet, of established and practical diagnostic value. There can, however, be no doubt that, in addition to their recognized theoretical significance, the practical value of skin tests in the diagnosis of infectious diseases is, on the whole, rapidly and continually increasing. There is surely no need to comment further here on the vast practical results which have followed the discoveries of allergic skin phenomena in diseases such as smallpox, diphtheria, and tuberculosis (Jenner, Schick, and Koch).

Among the more recent and important allergic skin-test reactions in infectious diseases, the reaction discovered by Frei (1929) in lymphopathia venerea has received general recognition. This specific diagnostic skin test has opened the door to the scientific study and to greatly advanced understanding of this not uncommon disease. Furthermore, the Frei test has welded into one entity many seemingly unrelated and idiopathic manifestations such as inguinal buboes, cer-

tain strictures of the rectum, elephantiasis and ulcerations of the genitalia, certain arthritic and febrile conditions, and certain multiforme and nodose skin eruptions.

The discovery of the Frei skin reaction was here literally epoch-making and has imparted a tremendous impetus to research into all phases of the disease lymphopathia venerea. The resultant great number of publications cannot be separately discussed here.

Complete and excellent reviews have been compiled by Hellerström[89] and by Wassén.[90] In these reviews, ample justice is done to the subject of skin allergy in lymphopathia venerea.

Wassén reports his own deliberate experimental infection of paretics with the virus. These experiments resulted not only in the production of lymphopathia chancres and buboes, but also of skin allergy demonstrable by the Frei test. The incubation period for the development of the skin hypersensitivity varied from several days to several weeks, appearing earlier in that group of individuals who reacted to the experimental inoculation with fever and with general systemic disturbances.

In the United States, ever since J. Wolf and I first employed the test in New York City, in 1931,[91] reports of proved cases of all forms of lymphopathia venerea have become more and more frequent; and these reports have come from all parts of the country. It is thus apparent that this disease is relatively common and widespread. An analysis of these reports indicates that the disease is most common among negroes, and more common among Latin Americans than among the native born in this country.

Sven Hellerström and E. Wassén[92] in 1930 and subsequently many others have shown that the brains of animals infected with lymphopathia virus may be used to prepare a vaccine which elicits specific skin responses in human beings and animals infected with the disease. Grace and Suskind,[93] in the United States, confirmed these results and reported their observations with mouse-brain skin-test material. Following Grace and Suskind's studies, such a mouse-brain Frei vaccine was made commercially available. A recent publication of Strauss and Howard[94] seems, however, to indicate that even normal, non-lymphopathia-infected mouse-brain will elicit positive skin-test responses on certain individuals, regardless of whether they have *lymphopathia venerea* or not. Aged preparations of mouse-brain are more likely to produce such false positive reactions. (Compare the skin-test excitant developing in aged cotton linters!)

It seems to be necessary, therefore, to employ a normal mouse-brain control when skin testing patients with infected mouse-brain material, in order to prevent confusion between reactions specific for lymphopathia virus and those produced from the mouse-brain tissues alone.

Since the publication of the list compiled by W. Jadassohn, several new specific skin reactions have been discovered in infectious diseases.

While W. Frei was, to my knowledge, the first to call attention to the possibility of such a reaction in tularemia, Foshay[95] was apparently the first observer to prove the existence and the value of the specific diagnostic skin test with *Bacillus tularensis.* The reaction is of the twenty-four- to forty-eight-hour tuberculin type so universally characteristic of the skin hypersensitivities produced by infections.

H. L. Baer,[96] among others, reports on the use and practical value of this test which becomes positive about two weeks before the agglutination test in the serum. As was to be expected in this tuberculin-type reaction, attempts at passive transfer gave negative results [personal communication]. In all these tuberculin-type reactions in infectious diseases, the attempts at demonstration of Prausnitz-Küstner antibodies are regularly unsuccessful.

My allotted space permits me to consider only a few of the many other contributions in the field of skin reactions in infectious processes.

One most recent and highly promising report of skin reactions to pneumococcus toxin must surely be included here, however. Coca,[97] together with Grove and Straus, reported positive specific skin reactions to soluble toxins produced by pneumococci cultured in media containing carbon dioxide.

This finding seems to be analogous, in many ways, to Schick's findings with diphtheria toxin, and its possibly far-reaching importance in pneumonia is therefore self-evident.

Among the newer immunologic studies of the skin responses in virus diseases, the studies of Hruszek,[98] and particularly of Biberstein and Jessner[99] must not be overlooked. While Hruszek employed mainly reinoculations with living virus, Biberstein and Jessner skin tested human subjects with a herpes simplex heat-killed vaccine.

Patients with recurrent herpes gave positive skin reactions, while patients with nonrecurrent herpes and normal subjects did not react. Repeated injections of the herpes vaccine exercised therapeutic and prophylactic effect in sufferers from recurrent herpes simplex.

Bargehr[100] has employed a lepra vaccine, and reports on the possibility of active immunization in leprosy.

Ray[101] reports on seven years' experience in the treatment of 187 cases of Oriental boil with a vaccine prepared from freshly isolated strains of *Leishmania tropica* grown on a solid culture medium. Of these, 151 patients were completely cured within from ten to twenty-eight days; 24 patients showed definite improvement; and 12 patients were unaffected by the vaccine treatment. The rapid and satisfactory

results in the majority of these cases, the lack of unpleasant by-effects, and the absence of disfiguring scarring make the vaccine treatment the one of choice in Aleppo boil.

In view of these eminently gratifying results in Aleppo boil, it seems to me that similar vaccine treatment is worthy of trial in the etiologically related kala azar.

Since the discovery of Finger-Landsteiner's law (1906), it has become more and more apparent that the course and manifestations of syphilis are intimately dependent upon variations in the specific tissue allergy. Skin superinfections in the various stages of syphilis in human beings and animals have demonstrated that the allergy of the tissues determined the development either of a secondary papule or of a necrotic and tubercular gumma; the result corresponding to the stage of the syphilis (secondary or tertiary) in which the superinfection was performed. Furthermore, the skin anergy to superinfection has been demonstrated in rabbits, both in a monoimmunity (strain specific) and a panimmunity (to all strains), and in the so-called period of chancre immunity, as observed both in laboratory animals and in human beings.

Experiments and investigations with luetin, and particularly with organ-luetin (Neisser and Meirowsky—1908), rather than with the culture luetin of Noguchi (1911), have proved the existence of a fairly regular and definite specific skin hypersensitivity in human beings in the late secondary and in the tertiary stages of syphilis, as well as in congenital syphilitics.

In certain stages of syphilis this skin reaction to luetin would seem to be of sufficient regularity to be of some limited practical diagnostic value. This point has frequently been emphasized. L. P. Barker[102] has recently studied this question with various organ-luteins, both in diagnosis and in treatment. Barker points out that, while his series of patients with gummas gave positive reactions in 77 per cent, there is an incidence of 3.5 per cent of false positives, i.e., reactions in non-syphilitics. John Stokes and others have called attention to these false positives to culture luetin. Barker again demonstrates the rôle of iodide and bromide ingestion in causing false positives even to organ-luetin skin tests.

It may be concluded that luetin skin tests are as yet of negligible practical value, in view of the present great accuracy of serologic diagnostic measures. Nevertheless, luetin tests have added a large fund to our accurate knowledge of the manifestations of skin allergy during the course of syphilitic disease; and the luetin results have corroborated the results of the superinfection experiments in demonstrating that allergic changes determine, to a great degree, the incubation, the course, and the morphology of the various stages of syphilis (W. Jadassohn).

TRICHOPHYTIN AND TUBERCULIN ALLERGY

These two forms of altered reaction of the skin are grouped together here because of their obvious close relationship and their many proved and well-known parallelisms. They are discussed as a separate group because these two specific allergies alone represent one of the principal fields of investigation in the problems of skin allergy.

It is probably that the study of the allergy of infection, i.e., the specific hypersensitivities, hyposensitivities, and immunities following infections, has nowhere received more attention than has been devoted to mycotic infections and to trichophytin allergy.

Br. Bloch's[103] brilliant summary of this vast field contains so much information regarding fundamental principles that no immunologist or allergist can afford to forego reading this contribution.

W. Jadassohn's[87] discussion of trichophytin allergy presents the entire status of the allergy of fungus disease, both in conjunction and in comparison with allergic manifestations in other infectious diseases and in noninfectious skin processes.

It may be regarded as proved that skin hypersensitivity to fungus extracts is based upon a specific, altered capacity to react, produced by infection or by other previous intimate contact with the microorganism. Not only the twenty-four- to forty-eight-hour tuberculin-type classic trichophytin skin reaction, but the innumerable other manifestations of mycotic allergy are closely analogous to the allergic phenomena and to the immunologic manifestations in tuberculosis. It is for this reason that the importance of studies in trichophytin allergy far transcends the importance of mycotic disease. The findings in trichophytin allergy parallel those in tuberculin allergy; and the results in fungus diseases can be applied *mutatis mutandis* to tuberculosis and also (to a great degree) to many other infections, notably syphilis, leprosy, and infectious granulomas in general.

As has been frequently pointed out, Koch's (and Lewandowsky's) experiments in guinea pig tuberculosis, and Bloch's experiments with fungi have demonstrated that the immunologic laws in these two diseases are essentially identical[87]; and, for many obvious reasons, it has been found advantageous to use studies in fungus immunology as a "model experiment" for investigating the immunology of tuberculosis.

It is certain, therefore, that attempts to reduce trichophytin hypersensitivity by means of repeated injections of trichophytin must be recognized as being of general interest far beyond that which they would merit were they considered strictly from the viewpoint of therapeutic undertakings in secondary fungus eruptions.

In 1930, Wise and I[104] reported successful reduction of trichophytin hypersensitivity in a series of cases of dermatophytosis and dermato-

phytids. In a study of cases with primary foci on the feet and secondary eruptions on the hands, we reported that repeated *intracutaneous* injections of increasing amounts of trichophytin reduced the tuberculin-like, forty-eight-hour reaction to trichophytin in the majority of instances. Moreover, these authors found that in some instances excellent therapeutic results accompanied the hyposensitization. These experiments were then extended to include hyposensitization by intracutaneous injections with combined trichophyton and monilia extracts, by Sulzberger, Pascher, and Kerr.[105]

Van Dyke, Throne, Kingsbury, and Myers,[106] who had carried on similar experiments at about the same time, were decidedly more enthusiastic concerning the therapeutic results. And recently Pennington[107] has submitted an extremely favorable report concerning the employment of the method advocated by Wise and me.

There are many other subsequent contributions from authors reporting varying degrees of success; and particularly favorable results are recorded by some authors who have employed greater dilutions (Krueger and Templeton[108]) and autogenous extracts (Robinson and Grauer[109a]; Scholz[109b]).

On the other hand, Traub and Tolmach[110] report unfavorably on the use of the original method, although they, too, were able to record 14 patients cured and 58 improved, some only temporarily, out of 135 patients treated with injections of trichophytin alone. Nevertheless, Traub and Tolmach confirmed the successful specific reduction of the tuberculin type response as reported by Sulzberger and Wise.

Wise[111] has discussed the present status of the therapeutic uses of trichophytin hyposensitization, and calls attention to the fact that he, together with George Lewis and me, is now engaged in studying the effects of the polyvalent and denatured trichophytin (claso-vaccine type of Jausion and Sohier) which is being enthusiastically recommended by da Fonseca and de Area Leao and their Brazilian collaborators.[112] This Brazilian trichophytin consists of over 300 strains of fungi, and is said to be denatured to such an extent that it no longer causes reactions, even in persons strongly hypersensitive to trichophytin. Our as yet unpublished observations, however, covering experiments on over 200 individuals, indicate that in general the Brazilian claso-trichophytin produces specific skin reactions in many instances, but often of lesser degree than those elicited by other and standard trichophytins. Thus, the excellent therapeutic results mentioned by da Fonseca and Leao in trichophyton, epidermophyton, and microsporon infections may be attributable, obviously, to trichophytin effect similar, at least, to that achieved with the older trichophytins.

It must be recalled in this connection that one specific skin-test-eliciting factor in trichophytin has long been known to be of nonprotein nature. This is one of the first specific carbohydrates, namely,

the nitrogen-containing polysaccharid isolated from trichophytin by Bloch, Schaaf, and Labouchère.[113] W. Jadassohn, Schaaf, and I[114] demonstrated the specificity and antigenicity of this polysaccharid of trichophyton fungi, both in man and in animals, by means of skin tests and Dale reactions, as well as with the Prausnitz-Küstner experiment.

It would seem that the question of the actual therapeutic efficacy of present methods of hyposensitization with fungus extracts must, at present, be answered as follows: (1) The method is effective in certain cases, and the theory of its action is to a great degree established. (2) The extreme difficulty of establishing the unequivocal diagnosis of dermatophytid, the unpredictable outcome of this hyposensitization method, and the irregularity of results in seemingly identical cases, make it necessary to restrict this therapy, for the present, to those cases which have resisted all other therapeutic approaches. (3) It is, nevertheless, an established fact that trichophytin hypersensitivity can be regularly reduced by repeated trichophytin injection. It is to be expected, therefore, that improvements in diagnostic measures, as well as variations in extracts and in hyposensitization technic, may lead to more uniform and satisfactory results in the therapy of fungus eruptions. (4) Through analogy with other infectious processes (and notably with tuberculosis), even the relative success of trichophytin hyposensitization should encourage renewed efforts to hyposensitization measures in different forms of tuberculosis; and in other chronic infectious diseases in which allergic manifestations are predominant factors.

It is to be noted here that the success of therapeutic hyposensitization in eczematous ids would be comparable to, and in some ways analogous with, the results of specific hyposensitization in eczematous eruptions in general, as previously discussed in reference to plant oils, etc.

Gradual hyposensitization by means of repeated injections of tuberculin has never ceased to be employed by many dermatologists in the treatment of certain forms of skin tuberculosis. Many European authors and, among others, MacKee in this country have reported on the efficacy of this measure. This therapy is distinctly indicated in certain forms of tuberculids and even in certain forms of lupus vulgaris, as an adjuvant measure.

Burnell-Jones[115] again calls attention to the indications for tuberculin therapy in tuberculoderms.

I have repeatedly pointed out the excellent effects of careful hyposensitization in tuberculoderms, and urged that the immunologic method of treatment deserves new and careful trial even in internal tuberculoses. This is especially urgent in view of the fact that hyposensitization with tuberculin came into early general disrepute mainly as a result of many severe and sometimes fatal reactions. In looking

for the reasons for these unfavorable sequelae, it must be remembered that, at the time of the early attempts at tuberculin therapy, little was known regarding the almost incredibly high degree of certain hypersensitivities; and little was known regarding the necessity for inaugurating hyposensitization treatment in such hypersensitive subjects by employing what, at that time, must have seemed to be ridiculously high dilutions.

I may here mention that it is not unusual for modern dermatologic treatment to begin with the intracutaneous injection of 0.1 c.c. of a 1:1,000,000 or even of a 1:100,000,000 dilution of O.T.K.; whereas the original dosage employed in treating internal tuberculosis was often from 0.1 c.c. to 2.0 c.c. of undiluted O.T.K.!

The present increased, not to say universal, interest in the skin reactions of allergy is to be welcomed. It will undoubtedly lead to the more general application of immunologic measures heretofore almost entirely limited to dermatologic employment (for example, tuberculin hyposensitization).

Regarding the recent nondermatologic literature on tuberculin-, luetin-, etc., immunology, many of these welcome contributions show that some of the new workers appear to have been grievously handicapped by the inaccessibility of the greater part of the fundamental and older dermatologic literature.

A. R. Rich[116a, b] and his collaborators have recently published a number of articles pointing out that the hyperergic inflammatory response to microorganisms and their products does not necessarily signify immunity; and that, vice versa, immunity can exist without such hyperergic reactions.

Unfortunately, these authors seem to have adopted a completely heterodox definition of the word allergy, for Rich and his coworkers seem to exclude from "allergy" specific, acquired immunity, a state which has always been regarded, to the best of my knowledge, as one of the cardinal manifestations of typical allergy (von Pirquet[1]).

It appears that the results and conclusions of these investigators are also subject to criticism because their experiments, however beautiful, merely prove what has long been an accepted fact, namely, that hypersensitivity of the tissues to tubercle bacilli and to tuberculin, to spirochetes and to luetin, to other microorganisms and their extracts in general, does not necessarily indicate an increased resistance to the respective disease.

Indeed, it has frequently been demonstrated and long been generally accepted that it is the very hypersensitivity of the tissues which —far from conferring immunity—often determines many of the severe manifestations of infectious disease.

On the other hand, what does require explanation is not the logical and easily demonstrated existence of immunity without hypersensi-

tivity, but rather the puzzlingly frequent simultaneous association of marked degrees of the admittedly harmful hypersensitivity together with definite manifestations of immunity (as remarked by von Pirquet, 1906).

It is no more than natural that dermatologists should have been among the first to recognize that allergic hyperergic inflammation in and of itself often exercises not a beneficial but a deleterious action upon the tissues of the host. The destructive lesions of tertiary syphilis, the destructive forms of lupus vulgaris, destructive iodo- and bromodermas, and many other destructive skin lesions are all attributable to the strength of the hyperergic allergic inflammatory response.

As J. Jadassohn and Lewandowsky have shown, and as since verified by numerous dermatologists and other observers, it is only when the severity of the allergic hyperergic response abates, and when tuberculoid structures appear—it is only then that the tissue begins to show evidence of immunity. In this tuberculoid phase the microorganisms have become scarce, are altered or are even absent; and, as the immunity increases, the inflammatory and sometimes caseating or true tubercles disappear, and so-called naked tubercles or sarcoid structures take their place. As a rule, no microorganisms can survive in these sarcoid reactions. At this stage of advanced resistance to the microorganisms, there is generally an advanced degree of resistance to their extracts; that is, a lack of reaction when the skin is tested by means of intracutaneous injections of the specific vaccines or extracts.

This is perhaps best illustrated by the so-called "specific or positive anergy" to tuberculin, which J. Jadassohn, Martenstein, W. Jadassohn,[117, 87] and many others have demonstrated to be the usual finding in tuberculoderms of the sarcoid group.

It has thus long been recognized that, not the allergic hyperergic inflammation, but rather the allergic lack of inflammatory response (specific anergy) was evidence of a high degree of resistance and immunity.

There are unfortunately few contributions in the English language on this fundamental subject. The most complete is probably that of J. Jadassohn, which appeared in the *British Journal of Dermatology*[118]; and, more recently, Wise and I,[119] and others, including Franz Blumenthal,[120] have contributed to the American literature on negative tuberculin reactions as evidence of tuberculous infection accompanied by allergy of the immune or specific anergic type.

POSSIBLE ALLERGIC FACTORS IN CERTAIN OTHER SKIN DISEASES

The possible allergic mechanisms in erythema nodosum and erythema multiforme have been the subject of numerous older and more recent studies. While there is increasing evidence that particularly erythema

nodosum may, in many cases, be due to allergy in tuberculosis,[121] the final word has not yet been said on this subject. It is evident, however, that skin reactions of the type of nodose erythemas and of multiforme erythemas are, in some instances, reactions of hypersensitivity to drugs, foods, virus, and microorganisms and/or their products

Many other diseases with skin manifestations have been studied with the possibility of allergy in mind. I shall mention here only such examples as lupus erythematosus (particularly of the acute disseminate type), psoriasis, lichen planus, pemphigus, periarteritis nodosa, dermatitis herpetiformis, and acne vulgaris.

The rôle of allergy has not been proved in any of these diseases, but it seems to me that the possibility of allergic mechanism in dermatitis herpetiformis and in acne vulgaris merits a brief discussion.

Since 1892 (Besnier and Doyon), dermatologists have noted and studied the hypersensitivity to iodine on the part of patients with typical dermatitis herpetiformis. This observation has been verified and studied by numerous observers, and it was shown by Danlos, Leredde, Engman, Kingsbury, Hallopeau, Dubois-Havenith, Levigne, Bechet, Krakauer, Angelo, Klepper, Laurentier, Greenbaum, and others that the administration of potassium iodide by mouth or subcutaneously produced dermatitis herpetiformis eruptions in certain predisposed individuals. In 1912, J. Jadassohn showed that the external application of potassium iodide ointment produced local reactions in a large percentage of dermatitis herpetiformis cases, although, as pointed out by Biberstein, Naegeli, Jessner, and others, the internal administration of even small doses elicited skin reactions in a higher percentage. In 1925, Jessner and Hoffmann showed that dermatitis herpetiformis cases were hypersensitive, not only to iodine, but also to bromine; and that they reacted to both external application and internal administration of potassium bromide in a large proportion of the cases.

This entire subject has subsequently received the attention of innumerable investigators, with confirmatory results.

A summary of this literature and reports of further original studies are submitted by Merfert[122] from Jessner's clinic. In addition to other interesting findings, Merfert records that in 132 cases of typical dermatitis herpetiformis, positive reactions to external application of potassium bromide or of potassium iodide were achieved in 86 per cent; while in 27 cases of pemphigus vulgaris, 23 were completely negative to these tests, and the remaining 4 were either only weakly positive or dubious.

This iodine and bromine hypersensitivity on the part of dermatitis herpetiformis patients is inexplicable, despite the possible relationship between the iodine effect and the much discussed and frequently con-

comitant thyroid and other endocrine dysfunctions in dermatitis herpetiformis patients. These demonstrated skin hypersensitivities to bromine and iodine, however, together with the common and often very high eosinophilia (I have seen as high as 55 per cent eosinophiles) favor the basic allergic nature of dermatitis herpetiformis.

It is here important to recall the effects of iodine and bromine ingestion on the luetin test, as mentioned in the previously discussed communication of L. P. Barker.[102]

Moreover, not only iodine and bromine hypersensitivity, but also hypersensitivity to foods may be demonstrated in some cases of dermatitis herpetiformis.

Sammis[123] has recently reported a case of presumptive dermatitis herpetiformis in an atopic individual. Here there were not only positive skin tests to foods, but it appeared that certain of the foods producing skin test reactions elicited clinical manifestations as well.

I have since seen a second severe and typical case of dermatitis herpetiformis in a nonatopic individual. In this case also skin tests with common allergens, including foods, elicited numerous definite reactions of the urticarial type.

These two isolated cases surely do not demonstrate that specific hypersensitivity to foods is of any significance in the production of the morbid entity dermatitis herpetiformis in general. Nevertheless, the sum of all the above findings in dermatitis herpetiformis calls attention to the possible factor of specific hypersensitivity, and thus demands that more cases be studied with this possibility in mind.

The well-defined and typical disease acne vulgaris cannot today be regarded as based upon any recognized form of specific hypersensitivity. Acneform drug eruptions due to bromides and to iodides, and perhaps also those due to other drugs or even to foods, may in some instances, however, closely simulate the picture of acne vulgaris. In the well-known oil, tar, pitch, and chlorine acnes, every one of the cardinal lesions of acne vulgaris may be encountered. In all these acnes of known external and internal etiology, either specific hypersensitivity or at least personal predisposition plays an acknowledged rôle.

In studying these acneform eruptions and their possible relationship to acne vulgaris, modern observers have considered the hypothesis of acne vulgaris based upon sensitivity of the pilosebaceous organs to metabolic products.

Rostenberg, Jr., Sher and the reviewer[124] have discussed this hypothesis, and alluded to the possibility of a follicular hypersensitivity to hormones. It would appear that the hormones connected with sexual maturation (anterior pituitary, gonad, and particularly the male and female sex hormones) would seem to be those most deserving of consideration in this connection.

A recent paper by B. Zondek[125] reports an observation which may be considered as supporting the hypothesis that a hypersensitivity of the pilosebaceous apparatus to the female sex hormone may be of significance in acne vulgaris. This author reports that local application of ointments containing gradually increasing amounts of sex hormone achieved "noteworthy results in young girls and in climacteric acne."

It does not require a stretching of the imagination to see a parallelism between Zondek's method and the recognized methods of local specific hyposensitization, as again reported by Kesten and Laszlo,[35] and by Maisel.[126]

It is no new observation that exacerbations in typical acne vulgaris cases may follow the ingestion of iodides, bromides, and certain foods such as chocolate. A recent article by Cleveland White[127] discusses the relation of food sensitivity to acne vulgaris. White frankly states that his observations are by no means conclusive; and in my opinion these experiments do no more than suggest that in certain isolated instances the ingestion of even common foods may produce acneform eruptions or may be followed by exacerbations of acne vulgaris. The value of this contribution lies more in its theoretical significance; although even from the practical viewpoint, the remote possibility of food hypersensitivity must be borne in mind in those cases of acne vulgaris or of acneform eruptions which have resisted all classic forms of therapy (x-ray).

ALLERGIC MANIFESTATIONS OF THE SKIN, WITH PARTICULAR REFERENCE TO THEIR SIGNIFICANCE IN GENERAL IMMUNOLOGY AND IN IMMUNOPATHOLOGY

The above heading includes all those observations in the skin which contribute toward the fundamental knowledge of immunologic manifestations as a whole. It is apparent, therefore, that many of the examples discussed under the other divisions of this paper could, with equal right, have been placed under the present heading.

The study and the observation of allergic skin phenomena have yielded information of incalculable value in all those aspects of biology and of medicine in which one encounters the manifestations of specific sensitization, hyposensitization, or immunization.

The obvious breadth of this subject makes it impossible for me to attempt a survey of the literally innumerable publications which merit attention. I must, therefore, confine myself to what must be a purely arbitrary selection of a few further contributions which have come to my notice.

One fact becomes apparent: workers in many branches of medicine and the allied sciences are growing more and more aware of the significance of the study of the skin in allergy. The advantages of em-

ploying the skin and its reactions in the basic studies of immunologic phenomena have long been apparent to dermatologists such as J. Jadassohn, Br. Bloch, W. Jadassohn, and their schools, as shown, for example, by the above mentioned observations on tuberculoid and sarcoid structures, and on specific hypersensitivity and specific anergy. Unfortunately, the results of dermatologic research into various aspects of allergy have appeared, to a great extent, in the special dermatologic publications. It is probably for this reason that the knowledge of the older dermatologic research has not become general property. Numerous examples of publications corroborating the earlier dermatologic findings appear in the nondermatologic literature of the last few years.

Kahn and McDermott[128] have brought additional evidence calling attention to the possible rôle of the skin as an immunologic organ or as site and originator of general immunologic effects. This is a concept well known to dermatologists, who have designated this manifestation by the term esophylaxis (Hoffmann, Alois Memmesheimer, Br. Bloch, etc.[132]). The experimental work of Bloch with fungus infections, and the work of many others, including that in arsphenamine sensitization, have brought experimental evidence which strongly suggests the possible important rôle of the skin in many processes leading to general hypersensitivity and/or immunity. The employment of the intracutaneous route for the administration of vaccines, allergens, and other agents designed to alter general reaction is based upon this concept. Percutaneous and intracutaneous immunization with tuberculin, with typhoid vaccine (Tuft), and with diphtheria toxin and toxoid (R. A. Kern, Crump and Cope) are some of the later procedures based upon this hypothesis; while one of the earliest observations pointing to the skin as an organ of great immunologic significance can be found in the pox vaccination of Jenner, which undoubtedly belongs to this group of phenomena.

Kline and Young[129] and other authors have again discussed reversible and nonreversible allergic inflammation. In the study of skin diseases, perhaps the greater number of allergic manifestations has always been recognized as belonging to the nonreversible group. I need cite here only such examples of nonreversible allergic tissue responses as seen in the Arthus phenomenon, in tuberculoderms such as lupus vulgaris, scrofulodermas, and erythema induratum; in the gummas of syphilis; in the destructive skin lesions of leprosy, sporotrichosis, blastomycosis, and in the mycotic granuloma of Majocchi (Kerion Celsi), etc.; and in the destructive and vegetating bromodermas and iododermas. These will surely suffice to support the statement that in the skin, at any rate, the nonreversible reactions of allergy are at least fully as frequent as the reversible forms.

Dienes and Simon[130] have recently confirmed the earlier observations of Biberstein, Frei, the reviewer[131, 132] and others regarding the genesis and nature of specific flare-up reactions seen in previously untreated animals and persons, and appearing spontaneously after a certain period of incubation at skin sites injected with foreign substances; or appearing in previously quiescent sites upon distant reinjection of the specific substance. These authors, in unanimity with previous observers, attribute the spontaneous flare-ups to the gradually increasing sensitivity of the skin, which eventually reaches a level which produces a reaction with the persistent deposit of antigen remaining at the injection site.

An editorial in the *Journal of the American Medical Association*[133] calls attention to the significance of these flare-up phenomena, and also to their possible relationship to nonspecific flare-ups. It is possible that some of these latter may find an explanation in the nonspecific elicitation of skin reactions in the Schwartzman phenomenon.[134] In this editorial no mention is made of the original dermatologic studies on the nature of flare-up reactions of all types.

Such flare-ups are regularly encountered by practicing allergists and dermatologists. They are frequently seen, for example, in the course of intracutaneous tuberculin or trichophytin hyposensitization, or when attempting to immunize patients who have previously been patch tested (as with ragweed[135]). It is not unusual to see areas of older patch tests or of older injections flare up suddenly after a later injection either of the same or even of another allergen. The nonspecific flare-ups are most frequently seen when trichophytin injection follows tuberculin injection, or vice versa. Frequent mentions of specific and nonspecific flare-ups are therefore constantly appearing in publications on dermatology and on allergy.

Another example in which observations of skin responses have aided in the clarification of general immunologic concepts is that of the possible production of hypersensitivity to autochthonous (homologous and autogenous) products.

Skin sensitivity to lens has again received attention; and its relationship to ophthalmitis phaco-anaphylactica has been discussed by Burky,[136] who advanced supportive evidence in the form of original animal experiments, employing as sensitizers a combination of lens extract and of staphylococcus toxin.

Woods[137] discusses the possibility that sympathetic ophthalmia may be due to a sensitization to the autogenous melanotic pigment of the eye and seeks to support this hypothesis through the evidence of skin reactions to tests with the uveal pigment.

Fully as fundamental as the above is the proof of the existence of sensitization to hormones, which was made possible through the demonstration of specific active and passive skin sensitization.

Collip's work was perhaps the first to direct general attention to the possible existence of antisubstances specifically directed against thyrotropic anterior pituitary hormone. This observer discusses the possibility that specific anti-anterior pituitary principles may exist and may be produced by repeated injections of anterior pituitary extracts. This work, however, does not here concern us directly, as it does not touch upon the question of skin reactions.

Evidence of existing hypersensitivity to hormones has long been the subject of clinical observation (e.g., intolerance to thyroid extracts on the part of patients with dermatitis herpetiformis, acne vulgaris, and, not infrequently, in others; intolerance to pituitrin injection [Hasson, Wang, Maxwell, and others]; the not uncommon intolerance to insulin, including the lysis of fat, etc.). While all these observations suggested the possibility of specific and allergic hypersensitivity, I believe that it was Tuft[138] who first brought unequivocal proof of specific hypersensitivity to a hormone. Tuft proved the existence of allergic hypersensitivity to insulin by means of skin tests and the demonstration of specific circulating Prausnitz-Küstner antibodies to this hormone.

Sammis,[139] in her most recent contribution, demonstrated that, in her case of insulin hypersensitivity, the reaction was directed toward the synthetic hormone itself; and that both skin reactions and passive transfer antibodies were specific for the hormone and were not directed toward any accompanying animal proteins or other accompanying impurities.

Simon,[140] and Simon and Ryder[141] studied human hypersensitivity to posterior pituitary extract in a careful and profound manner. By means of skin tests and other experiments in five cases of clinical hypersensitivity to pituitrin, they were able to show that, in this series, a constituent of the posterior pituitary, present not only in animal pituitary but also in human pituitary, produced immediate wheal reactions even in high dilution, and that there were no such reactions in controls. Specific passive transfer antibodies could be demonstrated in two of the five skin-hypersensitive cases. These observers point out that this hypersensitivity is directed to an organ-specific and not to a species-specific constituent of the pituitary gland of several species, including man. They conclude that this constituent is neither the oxytoxic nor the vasopressor principle.

It is surely unnecessary to point out to allergists that these studies demonstrating the existence of hypersensitivity to organ-specific autogenous products may be of incalculable significance in clarifying many hitherto obscure cases of what are apparently allergic conditions but which have stubbornly defied the discovery of an external cause. I refer to the well-known impossibility of finding external (or

internal) causes in many typical cases of perennial asthmas, vasomotor rhinitis, angioneurotic edemas, hives, eczemas, eczematoid and atopic skin eruptions, etc.

It may be necessary, however, to point out that such demonstration of specific immunologic alterations in tissue responses to hormones may exert a profound influence upon the science of endocrinology and the practice of hormonal therapy. This must be clearly apparent when one considers that the administration of hormones may exercise not only the substitution effects originally noted, but perhaps also produce antibodies which nullify the hormonal action, and which may even react in a depressor fashion upon the specific autogenous glandular substance in situ. One must even consider the possibility that hormones may act upon the specific organs they affect, in a varying manner, depending upon the degree of hypersensitivity or of hyposensitivity which the hormones administered may produce in the tissues of the end-organs susceptible to their action.

To put it briefly, these and similar studies may inaugurate a new science dealing with the immunology of hormones.

Among the many other examples of possible sensitization to autogenous products, I shall mention only the sensitization of mammals to a non-species-specific factor in mammalian serums, demonstrated by Simon[142]; and here again call to mind the previously discussed sensitization to autogenous serum reported by Bizzozero.

As mentioned above, I am forced to omit the discussion of many meritorious publications dealing with the truly fascinating study of general immunologic phenomena by means of observations of allergic skin manifestations.

In submitting this review, I feel that I must offer several explanations and apologies.

I have greatly exceeded my allotted space. I have permitted myself to do so because this is the first review of its kind to appear in the JOURNAL OF ALLERGY; and I therefore felt that some readers might derive advantage from the brief discussions of parts of the older dermatologic literature which forms the background of the newer contributions.

The objection may be raised that I have considered too wide a field to be the domain of dermatologic allergy. In reply, I can only say that the science of dermatology must embrace all manifestations in and of the skin, as well as all matters connected with these manifestations. This does not mean to say, however, that dermatology should consider these manifestations as its exclusive property. Quite the contrary. The skin offers, because of its visibility and accessibility, unparalleled opportunities for the study of phenomena of importance to all branches of medicine. Because of its exceptional rôle as a pos-

sible indicator of general allergy and of allergy in other organs, the skin must be a common meeting ground for allergists and dermatologists, and for all others occupied in the considerations of immunologic phenomena.

I feel that I must justify myself for having given free rein to so many expressions of purely personal opinion. None of my expressed opinions presumes to be final. I have attempted to present every opinion as objectively as it lay within my limitations to do so, and I have included these, my opinions solely, in the hope that some may serve to stimulate further study and discussion.

Before closing, I must again apologize, not only for the length of this communication, but also for its shortcomings. I have recognized from the very outset that I should be unable to do justice to more than a fraction of the mass of interesting material dealing with the subject assigned to me. I am conscious of the general inadequacy of this review of recent contributions to allergy in dermatology; and I particularly regret the necessary omission of numerous excellent articles which I have seen, and of the many others which have certainly escaped my notice.[143]

962 PARK AVENUE

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(f) Since the preparation of this compilation there has appeared the following excellent Review on Allergy in Dermatology: Stokes and Garner, Am. J. M. Sc., April, 1936.

Selected Abstracts

Asthma

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., CHICAGO

The Mechanism of the Paroxysm in Bronchial Asthma. Walzer, M.: Journal-Lancet **56**: 117, 1936.

Walzer discusses the mechanism for the bronchial stenosis in asthma. Arguments for the constriction or muscle spasm theory are: (1) the demonstration of bronchial constriction in animals as the result of vagus stimulation; (2) the hypertrophy of bronchial musculature in asthmatic lungs; and (3) the bronchoconstriction in anaphylactic shock in the guinea pig. The above arguments, according to Walzer, are not sound. Vagus stimulation has never been definitely linked with the mechanism of asthma. Hypertrophy of bronchial musculature can and does result from any effort on the part of the bronchi to overcome the effects of stenosis or because of the cough. While there is an analogy between anaphylaxis in the guinea pig and human asthma, there are so many differences as to question seriously the identity of the two.

The author sees more evidence for the theory that mucous membrane edema is responsible for asthma. In atopic manifestations such as hay fever, urticaria, eczema, and others, edema is the outstanding reaction. In the passively sensitized nose, eye, and rectum, edema was seen to be the mechanism involved in the reaction, and this also demonstrated the ability of these mucous membranes to fix reagins. Walzer suggests that we may be justified in assuming that the bronchial mucosa is also able to fix reagins. The prompt relief from the use of inhalations of adrenalin spray also argues for local effect on the mucous membrane. Walzer admits that there may be secondary bronchial spasm, but he contends that the chief and primary mechanism in asthma is probably a mucous membrane edema.

Interpretation of the Skin Test Used in Allergic Disorders. Alexander, H. L.: Journal-Lancet **56**: 131, 1936.

Alexander recites the difficulties in the path of those who would rely on the skin test in the causal diagnosis of a clincial allergy. Negative skin tests to allergens to which the individual is clinically sensitive are not uncommon. This occurrence is not difficult to understand when we ponder upon the common observation that localized allergy is the rule rather than the exception. Urticaria, for example, as the sole clinical manifestation of a food allergy signifies that the skin only (and in only some areas, at that) is sensitive to that substance, at least at the particular time and with that amount of allergen. Hence we need not be surprised that one may have a cerebral localization (migraine) and fail to have sufficient cutaneous sensitiveness to result in a positive skin test. "False positive" reactions may also be confusing. The author does not decry the use of skin tests but believes that they are of practical usefulness only in the hands of one who has had years of experience in their interpretation. For others he suggests either a limited use of tests and the substitution of clinical exclusion methods or the use of tests only in simpler allergies such as hay fever.

Relation of Asthma to Sinusitis. With Special Reference to the Results From Surgical Treatment. Cooke, R. A., and Grove, R. C.: Arch. Int. Med. **56**: 779, 1935.

In 248 cases of infective asthma whose age of onset was over ten years, sinus infection was found to be a causative factor in 92 per cent. The authors believe that an allergic reaction of the bacteria or their products is the cause of the infective asthma. As support of this idea they cite the occurrence of (1) a frequent familial history of asthma, (2) other allergic manifestations, (3) eosinophilic response of sinus mucosa, (4) eosinophile content of blood and nasal and bronchial secretions, and (5) the production of systemic reactions by vaccine injections. They believe that the demonstration of the latter phenomenon is much more diagnostic than the intracutaneous reactions to vaccines. Of 70 patients who were given vaccines, 38 had an asthmatic attack at some time or other following an injection.

Of 120 asthmatic patients with sinus disease who were treated surgically and subsequently observed from one-half to three and one-half years, 70 per cent showed improvement. In those with incomplete operations 39 per cent improved, while in those with complete surgery (ethmoids, sphenoids, and Caldwell-Luc where indicated) 86 per cent improved. No external operations were done. Striking results should not be expected too soon after the operation, but increasing improvement occurs with passage of time. The authors emphasize that associated sensitizations must not be neglected.

Recent Advances in the Diagnosis and Treatment of Allergic Disease. With Special Reference to Glucose Tolerance and Metabolism. Wilmer, H. B., and Miller, M. M.: Southern M. J. **29**: 197, 1936.

These authors found that the glucose tolerance curve in allergic individuals shows definite deviations from the normal chiefly indicative of a higher tolerance (lower curve). They conclude on the basis of such studies in 100 individuals that carbohydrate tolerance and metabolism are altered in the allergic state. It is suggested that the combined use of epinephrine and glucose is of value in refractory cases of allergy.

Treatment of Asthma With Ethylhydrocupreine. Service, W. C.: Colorado Med. **33**: 24, 1936.

In treating a postpneumonia asthma with ethylhydrocupreine Service obtained good results. This encouraged him to try this drug in other cases of asthma in which either the cause was undiagnosed or the allergic management was unsuccessful. He treated a group of chronic asthmatic patients with this drug giving 4 grains at 8 A.M. and 10 A.M. each with a glass of milk. This was done for two successive days. Then after an interval of two days a second course was given. After the latter the treatment was individualized, giving each patient the minimum amount of the drug required and as seldom as possible. Most patients remained free from symptoms after two months of treatment followed by an occasional dose. Sixteen patients were treated, of whom 11 have shown favorable results. The author mentions that care must be employed in the use of ethylhydrocupreine because of the toxic and serious symptoms that it may produce.

Hypochlorhydria in Asthma. With Special Reference to the Age Incidence. Gillespie, Marjorie.: Quart. J. Med. **4**: 397, 1935.

In a study of gastric acidity in 109 asthmatic patients by means of fractional test meals 51.5 per cent were found to have a low free acid and 41.2 per cent a low total. The hypochlorhydria was found to be more common in children under

the age of fifteen years and became less marked in young adults. It became more common again in those around middle age. Sensitivity, as determined by skin tests, apparently bore no relationship to the gastric acidity. It is also suggested that the increase of gastric mucus in these asthmatic patients may be due to a diathesis linked with allergy and that the mucus may in some way, perhaps by blocking the acid ducts, diminish the secretion of acid.

The Leucopenic Index in Intractable Asthma. Zeller, M.: Illinois M. J. **69**: 54, 1936.

Zeller reports on the valuable information given by the determination of leucopenic indices to foods in a small series of cases of intractable asthma. He found this method to have 21 per cent greater diagnostic value than the same number of skin tests with foods in this series of 12 cases. He warns that just as with skin tests it is possible to obtain false positive and false negative reactions with leucocyte counts. It is concluded that the leucopenic index is of much greater value than elimination diets.

Asthma From Dinitrophenol Sensitization. Noun, M. H.: J. Iowa M. Soc. **25**: 610, 1935.

A mildly allergic woman began to have severe asthma shortly after she started to use dinitrophenol. Elimination of the drug stopped the attacks. Oral ingestion or intradermal injection caused a relapse. Skin tests were definitely positive, and reagins were demonstrated on passive transfer.

A Newly Discovered Cause of Asthma. Biederman, J.: Ohio State M. J. **32**: 236, 1936.

The cause of the asthmatic attacks of a thirty-year-old woman was traced by Biederman to the fumes of lighted matches. By experimenting with the various ingredients of match tips he found that only the fumes of the phosphorous compounds (red phosphorus and sesquisulphide of phosphorus) produced the symptoms. Another patient, similarly affected, was found to be sensitive to the phosphorus and to the chlorate of potash. The author believes that there are many such cases and thinks that match fumes may be a common cause of asthma.

Hay Fever

UNDER THE DIRECTION OF W. C. SPAIN, M.D., NEW YORK CITY

Observation of Pollinosis in Lombardia in the Last Three Years. Part II. Sangiorgi, P.: I Quaderni dell' Allergia **2**: 12, 1936.

Seasonal periods of pollinosis are discussed by the author, the differences appearing in various countries, such as America, Egypt, India, Italy, Germany, and France being mentioned. Sangiorgi also enumerates the various hay fever producing plants which occur in central Europe. From the study of almost a thousand cases of hay fever, the author has found that the plants most commonly causing symptoms in Milan and vicinity are the *gramineae* (corn, oats, wheat, millet, barley, rice, buckwheat, dog's grass), which are responsible for 25 per cent of the hay fever cases; the *urticaceae* (nettle), also responsible for 25 per cent; the *iradaceae* (crocus, iris, sword grasses), 13 per cent; the *rosaceae* (rose family, as crab apple, apple, quince, medlar, plum, almond, pear, peach, apricot, cherry tree, hawthorne, blackthorn),

12 per cent. Many other plans are mentioned as producing hay fever. The willow, walnut, chestnut, oak, beech, birch, alder, lime, and linden trees have been found to be responsible for many cases. The tree season in Milan begins in late February with the pollination of the birch and alder, and continues until May. The grass season also begins in February, and extends through the summer into mid-October, reaching its peak in May and June. The author states that the majority of the people suffering from pollinosis in Milan have recurrences of their symptoms in April, May, June, and July.

The clinical varieties of pollinosis are as follows: spastic coryza, 70 per cent; bronchial asthma, 15 per cent; coryza and asthma combined, 7 per cent; respiratory pollinosis and dermatitis combined, 3 per cent.

In his study the author refers to the botanical families and not to the individual genera and species. He states that the cutaneous tests with the pollen extracts of every individual species present practical difficulties, represented by the fact that to perform these tests several hundred scarifications or intracutaneous injections must be employed in order to approximate a diagnosis. He realizes that his procedure is contrary to that employed in America. However, he believes that group reactions answer his purpose most satisfactorily. He points out that in most instances of clinical pollinosis there is present a multiple sensitization.

Serological Estimation of Allergens in Pollen Sickness in Respect to the Antibody Titer. Albus, Gunther: Ztschr. f. d. ges. exper. Med. **96**: 710, 1935.

Albus claims that the serologic estimation of allergens according to the method devised by him is of considerable importance, since it promises determination of allergic conditions which are not demonstrable by the usual cutaneous test. Furthermore, hypersensitive conditions having no clinical symptoms are said to be detectable by this means. He asserts that failure in specific desensitization with pollen extracts can be considerably lessened when his method is employed.

The author's method is as follows: 0.2 c.c. of active human serum, 1 c.c. of physiologic saline, and varying amounts of 5 per cent sheep corpuscle suspensions from 0.1 to 1.0 c.c. are mixed. After thirty minutes, at 37° C., the last tube showing complete hemolysis is determined. For the test a series of test tubes are set up. In addition to 1.2 c.c. of serum and the amount of sheep cells determined above, the antigen (pollen extract) is added in geometrically increasing dilution, in place of the physiologic saline solution. After thirty minutes at 37° C., a reading is made. The antibody titer (A-K) is the reciprocal of the dilution of the antigen giving partial suppression of hemolysis. Many extracts, i.e., pseudoacacia, have a high content of phytosterols which give false results.

The practical application of this method by the author is in the treatment of patients in whom pollen desensitization procedures have been used previously without encouraging results. Also, it is employed in the study of patients with negative skin reactions. If the test is negative in this latter type of patient, it should be repeated the following hay fever season only if no specific treatment has been given in the meantime. Since the antibodies are estimated by this method at the same time as the allergen, it affords a key to the prognosis, provided the previous antibody values of the patient are known.

On the Efficacy of Mixed Extracts in the Treatment of Pollen Allergy. Albus, Gunther: Ztschr. f. d. ges. exper. Med. **97**: 756, 1936.

Treatments were given to hay fever patients with preparations consisting of extracts of the pollens of the mixed grasses, to which were added linden and jasmine pollen extracts. By means of the author's test (as described in an accompanying abstract) which is based upon the inhibition of the hemolytic power of

patient's serum on sheep's corpuscles in the presence of pollen extracts, Albus concluded that though the various pollen extracts, as separate components of the mixed grasses, are greatly diluted in the mixture, they retain their full potency; furthermore, that nonallergic components which might be formed during the extraction have no power to produce an artificial allergen as shown by humoral antibodies or cutaneous reaction.

Modification of Antibody Concentration by Specific Desensitization in Pollen Allergy. Albus, Gunther: Ztschr. f. d. ges. exper. Med. **95**: 703, 1935.

The author states that while the procedure of immunization of hay fever patients with specific pollen extracts has been generally accepted, no satisfactory explanation of the mechanism has heretofore been offered. This he attempts to do. He describes experiments of his own to show definitely the effect produced upon the sensitive individual by specific therapy. This effect is demonstrated by the neutralization, by means of pollen extracts, of the specific antibodies present in the cells of the hypersensitive organism. The diminution in the antibody content thus produced prevents a general antibody-allergen reaction from occurring when the allergen again, subsequently, enters the hypersensitive cell.

The author states that in this manner the clinical allergic manifestation resulting from the general antibody-allergen reaction is prevented.

Management of the Patient With Pollen Allergy. Hinnant, J. M., and Evans, F. D.: Cleveland Clin. Quart. **3**: 113, 1936.

The authors present a general discussion of the problems in connection with the diagnosis and treatment of hay fever, based upon their experience in the Cleveland Clinic. In the vicinity of Cleveland the pollen of the silver maple is usually the first to be detected in the atmosphere, about the last week in April. It is closely followed by the elm, and later by the poplar and willow pollens. Oak pollen, considered by them as the most abundant and chief cause of tree hay fever, appears during May and is present well into June. Other important tree pollens are those of the ash, black walnut, hickory, sycamore, birch, and beech. The authors have not discovered sufficient plantain pollen to indict it as a noteworthy cause of summer hay fever. Timothy and the other grasses alone are considered of consequence.

The authors emphasize the need of individualizing the investigation and treatment in hay fever, and point out that respiratory disorders should always be searched for. They state that hypometabolism or true hypothyroidism is found in approximately 30 per cent of their hay fever cases. Routine blood counts, blood Wassermann tests, and blood sugar estimations should always be carried out. The red blood cell sedimentation rate is considered of value in frequent cases.

The authors advocate the scratch method of diagnosis, using the flexor surfaces of the arms for the pollen tests; they recommend the use of the back of the patient for the nonseasonal inhalants and foods, since ample area for a large number of tests is thus provided. One hundred and fifty to two hundred tests are completed, usually in two and in not more than three sittings, by these authors.

In their discussion of the various types of pollen therapy the authors state that, in their perennial cases, they give pollen injections once each week throughout the first year, treatments each fortnight or each month being too infrequent.

The Atmospheric Pollen in Montreal. MacDermot, H. C., and Howell, G. R.: Canadian M. A. J. **34**: 316, 1936.

The authors present a chart showing a daily ragweed pollen count obtained in Montreal for the late hay fever season of 1935.

They exposed slides daily from August 1 to October 12 upon the roof of an uptown apartment building. Their conclusion was that the pollen content of the air in Montreal increases after mid-August to a peak during the first week in September, and then decreases to disappear entirely by the end of the period stated.

Extraneous Factors Aggravating Seasonal Pollinosis. Rosenberg, Leon: M. Rec. **143:** 98, 1936.

The author attempts to explain the failures encountered in the treatment of seasonal pollinosis with pollen extracts, as often due to unrecognized sensitiveness to extraneous allergens, often of nonseasonal character, such as house hust, orris root, animal danders, etc.

The statement is made that the recognition and proper handling of this additional factor may correct these failures.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., BROOKLYN

The Disappearance of Specific Skin Hypersensitiveness in Tuberculosis. Paretzky, M.: Am. Rev. Tuberc. **33:** 370, 1936.

During a period of observation of two years, the author found 80 patients in whom the tuberculin cutaneous reaction disappeared temporarily or permanently. Intracutaneous tuberculin tests with as much as 10 mg. of tuberculin were performed before the hypersensitiveness was considered lost. The author attributes the loss of skin hypersensitiveness to retrogression of the infection and considers it indicative of favorable immunologic processes in the patient. The 80 cases were found in 67 families. They represented 5.9 per cent of the patients under observation. One and two-tenths per cent of the patients were under four years of age, 37.5 per cent between five and nine years, 36.3 per cent between ten and fourteen, 10 per cent between fifteen and nineteen, and 5 per cent over twenty. Among twenty-one cases starting with a negative reaction in which hypersensitiveness developed and then disappeared again, the minimum time for this entire course of events was nineteen months, the maximum fifty-five months, and the average thirty-four months. The disappearance of sensitivity was usually a gradual process. In 11 of 67 families, loss of sensitivity occurred in more than one member of the family, and in seven of these families this loss occurred simultaneously in several individuals. In 21.2 per cent of cases the hypersensitiveness reappeared. Analysis of 180 members of these families seems to indicate the presence of some hereditary features of immunity in tuberculosis.

The Development of Foreign Protein Sensitization in Human Beings. Mote, J. R., and Jones, T. D.: J. Immunol. **30:** 149, 1936.

While studying skin sensitivity to streptococcus proteins in rheumatic fever using filtrates derived from rabbit peritoneal fluid, the authors became interested in the various types of cutaneous reactions to rabbit serum which developed in these patients. After repeated intracutaneous tests at varying intervals with normal rabbit serum they found reactions appeared immediately or were delayed for twenty-four hours. The twenty-four-hour delayed type of reaction was usually the first to develop. Later in the course of sensitization an immediate reaction frequently appeared preceding the delayed type. In the more sensitive subjects, hypersensitiveness progressed to the stage where only an immediate swelling developed

without a subsequent delayed reaction. In only a few instances did the immediate type fail to be preceded in development by the delayed type of reaction; 51.9 per cent of cases developed, in addition, a reaction five to eleven days after injection, corresponding to local serum disease. Of sixty-nine subjects in the series 82.6 per cent developed some form of cutaneous hypersensitiveness to rabbit protein. In the regression of the hypersensitiveness the immediate type of swelling was the first to be lost, and later the delayed reaction also disappeared.

Search for antibodies in the blood in the twenty-four-hour type of reaction revealed none to be present. In the immediate type of reaction Prausnitz-Küstner antibodies were occasionally found and precipitins only infrequently.

The Route of Ingested Egg White to the Systemic Circulation. Alexander, H. L., Shirley, K., and Allen, D.: J. Clin. Investigation **15**: 163, 1936.

By means of precipitin tests and the Prausnitz-Küstner technic, the authors investigated the channels by which unaltered egg protein reached the systemic circulation of dogs following its oral administration.

Two or three hours after a meal of egg white, specimens were collected from the anesthetized animals. Lymph was obtained from the thoracic duct above the diaphragm, and blood specimens were taken from the portal vein and from the aorta. As controls, lymph and blood specimens were taken from five dogs fed on raw beef. Precipitin tests were prevented in three instances by the cloudiness of the lymph. They were strongly positive for egg white with five specimens of lymph and absent with one. With the systemic bloods precipitin tests were positive in six dogs and negative in three. With the portal bloods the precipitin tests were all negative.

With the Dale technic, employing the sensitized guinea pig uterine strip, positive muscular contractions were obtained when the systemic and lymph specimens were used as the test antigens. Results with portal bloods were negative. Skin tests with the Prausnitz-Küstner technic, using the various dog specimens as antigens, showed strong positive reactions with the lymph and smaller reactions with the systemic bloods. With the portal bloods no greater reaction was obtained on the sensitized site than on the control site.

All the control serums obtained from the beef-fed animals gave negative reactions for egg white with all the above technics.

Studies in Urticaria. V. The Effect of the Oral Administration of Certain Substances Upon the Experimental Wheal of Alimentary Origin. Walzer, Abraham: Minutes of the Ninth International Dermatologic Congress, Budapest, August, 1935.

To induce the experimental immunologic wheal the author used for sensitization 0.01 c.c. of a serum containing reagins for peanut. This was introduced intracutaneously in the subject and the result measured at twenty minutes to indicate the normal cutaneous response to the serum. Thirty minutes after sensitizing, the subject was fed the peanut meal. When the immunologic wheal developed five to fifteen minutes later at the sensitized site, the time of onset was noted and the reaction was also measured at twenty minutes. With this reading as an index of the subject's normal absorption response, the experiment was repeated at weekly intervals but in each instance kaolin, dilute hydrochloric acid, liquid petrolatum, or peptone was given one-half hour before the peanut meal. It was found in almost all instances that the immunologic wheal was slower in starting, but that it was usually larger than in the control studies. This increase in size was proved to be the result of the delay in the absorption of the protein following the use of medications. This delay gave the sensitizing reagins a longer period to fix and therefore resulted in a larger wheal than normally.

In experiments in which spiritus frumenti was administered with the protein meal it was found that the immunologic wheal was more rapid in onset and also larger than normal. In this instance it was proved that the increased size of the wheal was the result of an increased amount of protein absorption. The author believes that these experiments may possibly explain the beneficial effects obtained in some food urticaria when dilute hydrochloric acid, kaolin, liquid petrolatum, and peptone are administered. He also demonstrates experimentally the injurious effects of spiritus frumenti in these cases.

Dermatology

UNDER THE DIRECTION OF MARION SULZBERGER, M.D., NEW YORK CITY

Reactions Due to Phenolphthalein. Abramowitz, E. William: Arch. Dermat. & Syph. **31**: 777, 1935.

In reviewing the literature on cutaneous and general reactions to phenolphthalein, Abramowitz concludes that most of the former and some of the latter occur after a single or occasional average dose of the drug. Age does not seem to be a significant factor, as the reactions occur both in adults and in children. The laxative dose of the more highly refined white phenolphthalein is three times as great as that of the yellow phenolphthalein, which contains "dark bodies" possessing purgative properties. In no case could phenol, phthalic anhydride, and various derivatives or aromatic compounds related to phenolphthalein be held responsible for the cutaneous lesions. Nor did the blood or urine show any significant changes after use of the drug in normal persons. Whereas in normal subjects the drug is nontoxic, in persons once affected by a reaction of hypersensitivity to the drug even a very small dose may produce symptoms. In patients in whom the eruption follows an apparently initial dose, it is probable that they have been previously exposed to the drug in some unsuspected substance, for it may be present even in such unsuspected sources as dentrifices or cookies. Sensitization in utero is also possible owing to ingestion of the drug by the mother during pregnancy. Occasionally but infrequently a person suffering an eruption from this drug becomes desensitized, and on renewed administration no eruption develops. Experiments with autoplastic skin grafts seem to indicate that a fixed eruption represents local cutaneous hypersensibility, which can be reproduced at will by the specific excitant. Persons having suffered phenolphthalein eruptions probably develop an allergic form of specific hypersensibility. Likewise in the general reactions not due to overdosage or cumulative action of the drug the manifestations may be due to a similar sensitization of other tissues.

Influence of Drugs on Experimental Ursol Sensitization in Animals. Marquardt, F.: Arch. f. Dermat. u. Syph. **171**: 430, 1935.

Marquardt studied the effect of subcutaneous and intramuscular injections of adrenalin, pilocarpine, morphine, luminal, and thyroglandol upon the course of experimental sensitization with ursol (paraphenylendiamine) in guinea pigs of similar age and light color, and kept on the same diet during the experiment. The animals were sensitized to ursol by rubbing ursol vaseline into the shaved skin. Injections of large doses of adrenalin during the period of sensitizing activity of the ursol prevented sensitization, but the injections did not exert such an effect if delayed until after the contact with ursol had been prolonged. Likewise pilocarpine increased hypersensibility only if injected during the latent period. Atropine does

not diminish hypersensitivity in guinea pigs, probably because of the fact that guinea pigs are not very sensitive to this drug. No effect on the course of sensitization could be demonstrated as a result of injections of morphium-scopolamine, luminal or thyroglandol, excepting a transitory weakening effected by luminal.

Tuberculin in Treatment of Cutaneous Tuberculosis. Burnell-Jones, H. S.: Brit. M. J. 1212, June 15, 1935.

It is still uncertain whether lupus can be cured by tuberculin, but further investigations are encouraged by the improvement obtained in some cases. The author reports three cases that had persisted over a long period before tuberculin treatment was attempted. In one case improvement continued in spite of marked allergy. The fact is emphasized that the site of injection may determine the type of reaction. Thus in some patients reacting to local injections in the arm, no reaction results if the injection is made between the shoulders. The quantity injected is increased by 10 per cent at each dose and the dosage increased only if the patient does not react with a rise in temperature or unpleasant general symptoms. Patients differ widely in their tolerance to tuberculin. In the beginning small doses are administered twice a week. In the cutaneous cases the author preferred one injection per week and used smaller doses than for the pulmonary cases. If the tuberculin injections have to be temporarily discontinued, injections of diluting fluid only are continued. By this means, the patient may be kept under observation and is not discouraged by the cessation of treatment, and it is also possible to ascertain whether the rise in temperature is caused by the tuberculin or whether it is a nonspecific effect or a spontaneous fluctuation.

Cutaneous Test of Syphilis and Its Significance for Diagnosis and Treatment. Stein, R. O.: Indian J. Ven. Dis. **1**: 96, 1935.

Muller-Brandt has rendered available a new extract known as luotest for skin tests in syphilis. According to the present author, it is the first reliable specific preparation available for this purpose. Plammer reported positive reactions to luotest in 80 per cent of 106 cases of tertiary syphilis with various gummous lesions. The reaction becomes manifest as early as twenty-four hours after injection, appearing first as a brown papule surrounded by a red zone 1 cm. wide which attains the size of a silver dollar within from thirty-six to forty-eight hours. For diagnostic purposes a circumscribed red area with infiltration at its center constitutes a positive reaction. The infiltrate may be erythematous or papular. A negative reaction definitely excludes gumma, malignant syphilis, and congenital syphilis. In the latent stage of tertiary syphilis a negative Wassermann reaction may turn to positive shortly after the intense inflammation caused by the intracutaneous vaccine subsides. The genetic relation between the serologic reaction and the positive cutaneous reaction is considered as definitely demonstrated. Reactivation is due to activation of latent syphilitic foci, similar to the effect noted in cases of tuberculin reaction and trichophytin reaction.

Elementary Bodies of Zoster and Their Serologic Relation to Varicella. Amies, C. R.: Brit. J. Exper. Path. **15**: 314, 1934.

The results of Amies' experiments confirm Paschen's findings of elementary bodies in zoster vesicle fluid. Pure suspensions of these bodies are agglutinated specifically by zoster convalescent serums and the evidence presented suggests that the zoster elementary body is the etiologic agent of zoster. As regards the relation of zoster to varicella, cross agglutination tests did not give such uniform results as those obtained by the complement fixation method. Nevertheless the author believes that the high degree of specificity of the reaction lends significance to the positive results obtained.

As monkeys hyperimmunized with human variola virus develop antivaccinal agglutination and hyperimmunized antivaccinal serums from rabbits will agglutinate variola elementary body suspension, the failure to obtain cross agglutination in some of the present series of experiments may be explained in a similar manner. Recently Craigie demonstrated that a soluble antigen is responsible for the vaccinia flocculation reaction. This substance may be the same as the heat-stable precipitating substance isolated from autolysates of neurovaccinia rabbit testicles by Wilson Smith. Probably complement fixation reactions with zoster and varicella vesicle fluids depend more upon this soluble substance than upon the presence of intact bodies themselves.

Flaring Up of Injection Sites in Allergic Guinea Pigs. Dienes, L., and Simon, F. A.: J. Immunol. **28**: 321, 1935.

The authors describe observations made on guinea pigs injected intracutaneously with human serum and turtle egg. In guinea pigs as in man, the flares are unquestionably of the delayed type and develop at the moment when the guinea pig begins to give a delayed type of reaction to skin tests. Intravenous injections at this time cause no noticeable shock or temperature reaction. The nature of the antigen plays a considerable rôle in sensitization, and in the appearance or absence of flares both in man and in guinea pig. With egg white and horse serum, the authors have never seen flares in guinea pigs, although they produce strong sensitiveness. Human serum produces flares in about one-fourth of the animals treated, while turtle egg is effective in nearly all.

The influence of allergy on the development of early lesions receives support from observations here described. It is reasonable to assume that a portion of the antigen remains in the tissues in a latent condition, and when the sensitization appears in the skin, a slowly developing inflammatory reaction characterized by mononuclear infiltration begins. Microscopic study of the flares shows an infiltration with mononuclear cells. The incubation period and the type of microscopic structure show many analogies to certain infectious lesions. As allergy develops both after infection and after treatment with turtle egg, it probably exerts an analogous effect on the development of the similar lesions in both. The appearance of an exanthem in a guinea pig injected with a large dose of human serum presents many analogies to human serum sickness, with the difference, however, that the exanthem is not fleeting but exists for several days.

The difference between delayed and immediate reactions is certainly not simply quantitative, but the whole reaction mechanism is different; identification of the two types does not seem possible. The nature of the difference between the exanthem observed in guinea pigs and that in human serum sickness cannot, at present, be interpreted. It is suggested that the developing allergy probably plays a rôle in the development of specific tissue reactions in lesions of certain infectious disease.

Factors Affecting Color of the Skin. Their Significance in Berlock Dermatitis. Rogin, James R., and Sheard, Charles: Arch. Dermat. **32**: 265, 1935.

The authors undertook the following experiment to test the concept that oil of bergamot sensitizes the skin to sun rays and thus leads to pigmentation. The following three sites were exposed to rays of a sun lamp: (1) skin site covered with oil of bergamot; (2) site covered with 10 per cent tincture of oil of bergamot; (3) an untreated (control) site. The three sites were regularly examined over a period of four to five weeks with the spectrophotometric system. It was found that the treated sites evidenced decreased sensitivity to sun rays and showed no more erythema or pigmentation than did the untreated site. It was concluded that berlock dermatitis is due to an individual hypersensitivity to chlorophyl or to perfume ingredients.

Otolaryngology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

Cytologic Examination of Nasal Smears of Sensitized and Non-sensitized Persons With Nasal Symptoms, With Special Reference to the Eosinophile Count and to Simultaneous Blood Counts. Cowie, D. Murray, and Jiminez, Buenaventura: Arch. Int. Med. **57**: 85, 1936.

The value of the determination of the cytology of the nasal secretions in allergic and nonallergic individuals with nasal symptoms is exemplified in the extensive observations of Cowie and Jimenez. The cytology of the nasal secretions was studied in allergic individuals free from infectious colds. Such types as pure hay fever, hay fever plus other sensitivities, multiple sensitization but not to pollen, and sensitization with an associated epidermal sensitivity were considered in one group. The second group of cases consisted of sensitized persons in whom the cytology of the nasal smears was studied during the period of infectious colds. Comparative simultaneous differential counts of the blood and nasal secretions were also made. On the basis of these studies the authors state than an eosinophile count in a nasal smear of from 20 to 25 per cent indicates that the patient is allergic. The percentage of eosinophiles seems to be greater in patients with epidermal sensitization. During an infectious cold, it was found that the neutrophiles predominate in the cytologic picture with or without varying percentages of eosinophiles. Comparative simultaneous differential counts of the blood and nasal smears did not show a definite relationship to each other. Attention was called to the fact that the typical, pale, boggy, mucous membrane may not be present in nasal allergy but eosinophiles may be demonstrated in the nasal secretions.

The computation of the number of eosinophiles and neutrophiles in nasal smears in terms of percentages is subject to considerable discrepancy unless the cellular distributions are uniformly even. For example, the clumping of eosinophiles in masses in the presence of a large number of eosinophiles is not infrequently noted in cases of nasal allergy with acute infection. Although the cytologic picture may be diagnostic of allergy, the relative proportions of the two types of cells in terms of percentages may not be significant. Considerable variation in the relative numbers of eosinophiles and neutrophiles occurs, dependent upon the particular stage of an acute rhinitis superimposed upon an allergic process. During the early stage of a cold, the neutrophiles may completely predominate the picture. As a rule, the number of eosinophiles shows a significant increase in the late stage of the cold when the neutrophiles are beginning to disappear.

Endophthalmitis Phaco-anaphylactica, A Clinical Study. Goodman, E. Leonard: Arch. Ophthalmol. **14**: 90, 1935.

Goodman has made a very extensive study of hypersensitivity to lens protein in a group of 700 unselected patients with cataract who were admitted to the Wills Hospital during 1932. Approximately 5 per cent of the 700 patients tested intracutaneously with bovine lens antigen were found to show reactions of two-plus or greater and were regarded as being truly hypersensitive to lens protein. He believes that hypersensitivity to lens protein is acquired and is not congenital. Cataractous cortical material forms the principal antigenic factor. Hypersensitivity to lens protein occurs only in patients with diseases of the lens. No relationship was found between diabetes, syphilis, or asthmatic and hay fever allergic states and the production of autosensitization to lens protein. Attention is called to the fact that when lens material is left in the eye of non-sensitive individuals it is not so

great a source of danger as it is when left in the eye of a sensitive patient. It was also noted that the amount of lens material remaining in the anterior chamber after operation is, in general, in direct ratio to the degree of postoperative reaction, whether in sensitive or non-sensitive individuals. It is also stated that lens material left in the eye following operation may have a deleterious action because of its toxic mechanical or anaphylactic properties, the latter being productive of the most severe types of reactions. A combination of the above three modes of action is also to be taken into consideration. Desensitization to lens protein is advocated before operation in hypersensitive individuals. Desensitization during the active stage of endophthalmitis phaco-anaphylactica is not considered advisable. Goodman advocates the attempt at intracapsular extraction in all favorable cases when there is any reaction to the cutaneous test with lens protein. In the event of a rupture of the capsule, thorough irrigation of the anterior chamber to remove all cortical material should be carried out.

Manifestations of Nasal Allergy: Their Diagnosis and Treatment. Jay, H. M.: Brit. M. J. 2: 833, 1935.

In a general discussion of the subject of nasal allergy, Jay calls attention to the diagnostic difficulties sometimes encountered in the recognition of these cases. The typical picture of a pale, boggy mucosa is not infrequently absent; therefore a great deal of dependence must be placed upon an accurate clinical history. The nasal manifestations of allergy should always be considered when dealing with patients with frequent colds, catarrh, and nasal obstruction. Jay emphasizes the importance of making a distinction among the following types of cases: (1) polyposis due to allergy, (2) polyposis due to infection, and (3) polyposis associated with allergy and infection. He adopts a conservative attitude toward surgery and points out that patients selected for operative interference should be carefully selected. He places primary importance upon the recognition and treatment of the allergic process.

Sinusitis Allergy and the Common Cold: A Conception of Their Relationship. Sewall, E. C.: Arch. Otolaryng. 22: 425, 1935.

The relationship of sinusitis allergy and the common cold was discussed by Sewall, who called attention to a number of important points in bacteriology and pathology. Acute infectious rhinosinusitis, chronic infectious rhinosinusitis, and chronic hyperplastic rhinosinusitis were all considered from these viewpoints. The importance of distinguishing the nasal manifestations of allergy from these various types and the recognition of combined forms of allergy and infection were emphasized.

Allergy in Oto-Rhino-Laryngologic Practice. Watkins, A. B. Keith: J. Laryng. & Otol. 50: 310, 1935.

That the rhinologist has become allergy conscious in the diagnosis of sinus diseases is exemplified in many recent discussions of this subject. For example, Watkins emphasizes that allergic phenomena are very common in nasal diseases and are likely to be overlooked unless careful history-taking and examination are instituted. He further states that the failure to recognize the presence of allergy is responsible for lack of success in many operations on the nose. The relation of nasal polyps to allergy and the association of infection with nasal allergy were also discussed. The importance of the primary consideration of the allergic process before instituting operating procedures is advised.

Pediatrics

UNDER THE DIRECTION OF FRANCIS S. SMYTH, M.D., SAN FRANCISCO

The Treatment of Asthma With Whole Suprarenal Gland. Barbour, O.: Arch. Pediat. **53**: 203, 1936.

The author reported the oral administration of suprarenal and thyroid gland for the prevention and treatment of asthma. Observations were made on 112 infants and children over a period of five years. Vasomotor rhinitis accompanied the attacks in the majority of patients, and neosynephrine 1 per cent was used to keep the nasal passages open and seemed to contribute to the welfare of the patients. The regime was continued for several weeks with apparent diminution of the asthma. The author does not consider skin tests or elimination diets worth while.

Immune Reactions Induced in Infants by Intestinal Absorption of Incompletely Digested Cow's Milk Protein. Lippard, V. W., Schloss, O. M., and Johnson, P. A.: Am. J. Dis. Child. **51**: 562, 1936.

Four hundred and sixty complement fixation tests for lactalbumin were performed on the blood of 229 normal infants, children, and adults. These tests showed the presence of lactalbumin in the infant's blood within a few days after its first ingestion, reaching its greatest frequency from the fourth to the twentieth day. Thereafter it diminished rapidly. Specific cow's milk antibody tests also showed the appearance of these antibodies in from eight to fifty days and persisted for several months. This report is a very valuable contribution to the theoretical aspects of milk sensitivity and allergy.

Miscellaneous

Functional Activity in the Experimental Production of Hyperergic Coronary and Pulmonary Arteritis. Knepper, R., and Waller, G.: Virchows Arch. f. path. Anat. **294**: 587, 1935.

Klinge and others have shown that an allergic reaction in the coronary arteries histologically like that seen in acute rheumatic infection may be produced provided large amounts of antigen are used. In the experiments here reported, rabbits were given horse serum or swine serum subcutaneously. They were then exercised vigorously in an electric treadmill in order to increase functional activity of cardiac and pulmonary tissues. In animals so treated, intravenous injections of comparatively small amounts of antigen (2 c.c. to 3 c.c. as compared to some 10 times this amount in Klinge's experiments) were sufficient to cause a typical hyperergic inflammatory reaction in branches of the pulmonary and coronary arteries.

Physiopathologic Study of Allergy to Ricin. Worinter, P., Grabar, P., and Koutseff, A.: Compt. Rend. Soc. de Biol. **118**: 60, 1935.

There appear in the literature about 50 cases of sensitiveness to ricin. These include laboratory workers with this substance, millers, and those living in an atmosphere charged with ricin dust, especially those engaged in decortication of grain. The route of entrance to the body is through the lungs. The affected person, who breathes in particles of ricin, suffers the respiratory form of allergy. In other instances the manifestations are ocular. Here a violent conjunctivitis with great edema follows minute amounts of the dust entering the eye. Occasionally an in-

tense cutaneous edema urticarial in type develops in different parts of the body, particularly on the neck, or about the collar, or on the face. All these occurrences are of short duration and last but a day.

The skin and mucous membranes of these allergic individuals react in a characteristic way. Rubbing an extract of ricin on the intact skin induces after five or ten minutes the formation of small edematous papules. A skin test by the scratch method gives a typical wheal. An intradermal injection induces a violent reaction even when very high dilutions are used. Patch tests are always negative. Instillation of one drop of very diluted extract in the eye is followed by a marked conjunctival reaction. The application of a tampon moistened with the solution of ricin provokes a marked rhinorrhea when placed in the nose.

The authors have demonstrated the presence of a specific antibody in the blood of three patients by means of passive transfer. This reaction was strongly positive in one case, negative in the other two. Eosinophilia was not present.

An exposure of many months or even of a year seems necessary in order to induce allergy to this substance. On the other hand, there are normal subjects who, having worked for years with ricin, gave no skin reaction.

Allergy and Vitamin C. Hochwald, A: Zentralbl. f. inn. Med. **56**: 769, 1936.

In order to investigate the effect of vitamin C on allergy, the author chose anaphylactic shock in guinea pigs as a method, although he was aware of the distinction between such a reaction and allergy in human beings. He injected guinea pigs sensitized to human serum at intervals between ten minutes and two hours with 100 mg. of ascorbutic acid (before the intracardial shocking dose). The optimum dose proved to be two injections forty-five and fourteen minutes before the serum injection. Of 29 guinea pigs so treated, 9 went into immediate shock, 2 had mild shock, and 18 had no symptoms. Of 20 control animals, 18 went into shock.

The antianaphylaxis obtained was not due to storing up of vitamins in the body, for in experiments wherein vitamin was given from two to two and one-half hours before serum injection, there was no effect on shock, and all animals died. Ascorbutic acid injected before the sensitizing dose likewise had no effect.

Similar protection was attempted against histamine shock but was not successful. When 150 mg. glutathione were injected forty-five and fifteen minutes before the shocking dose, 7 out of 11 pigs survived.

Although the author is unwilling to commit himself concerning the mechanism involved in the protection secured, he believes it due to an effect on the reticuloendothelial system, which is blockaded. This mechanism is similar to the protection against anaphylactic shock secured by certain colloidal substances.

In closing, the author mentions that he has treated allergic conditions in human beings with startling effect, which he will report on later.

Book Review

IMMUNOLOGY. BY NOBLE PIERCE SHERWOOD, St. Louis, 1935, 570 pages, illustrated, The C. V. Mosby Co.

On a topic advancing as rapidly as that of immunology, textbooks soon lose much of their usefulness. Consequently, a new work by an author as well informed as Dr. Sherwood, who brings the subject up to date, is a valuable acquisition. The book deals with the entire field of immunology. The last one hundred pages, about one-fifth of the text, are devoted to hypersensitiveness.

The problem of anaphylaxis is stated and developed in a conventional manner. This is followed by the important consideration of hypersensitiveness due to infection, particularly allergy in tuberculosis. Finally, human idiosyncrasies are taken up, a chapter which includes, briefly, clinical manifestations, the tests used, and mention of treatment.

Although space devoted to the various aspects of the subject is necessarily limited to a brief description, an extensive bibliography is appended to each chapter. Such an arrangement conforms to the best type of textbook, which after all is but a guide to students and which states the problems concerned and points to where authoritative literature may be found. The references given are well chosen.

This is a book of reference which well serves its purpose.